

## ORIGINAL STUDIES

# Systematic Review and Meta-analysis of Postlicensure Observational Studies on Human Papillomavirus Vaccination and Autoimmune and Other Rare Adverse Events

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**Background:** Because of the limited number of subjects in prelicensure studies, autoimmune diseases and other rare adverse effects of vaccines may go undetected. Since 2006, millions of human papillomavirus (HPV) vaccine doses have been distributed and a considerable amount of postlicensure safety data has been generated. The objective of this study was to review available HPV postlicensure safety studies and to summarize risk estimates of autoimmune and other rare diseases.

**Methods:** For this systematic review and meta-analysis, we searched literature databases to identify any postlicensure safety studies related to HPV vaccination and autoimmune adverse events from inception to April 16, 2019. Pooled risk estimates were computed using fixed- or random-effects models if at least 2 estimates per disease and per HPV vaccine were available.

**Results:** Twenty-two studies met our inclusion criteria. The studies applied various methodologies and used different types of data sources and outcome definitions. Quadrivalent HPV vaccine (4vHPV) was most commonly assessed. Type 1 diabetes mellitus, immune thrombocytopenia purpura and thyroiditis diseases were most frequently reported. The meta-analysis was conducted on 35 diseases corresponding to 48 pooled risk estimates. Majority of the pooled estimates showed no significant effect ( $n = 43$ ). Three negative (paralysis, immune thrombocytopenia purpura and chronic fatigue syndrome) and 2 positive (Hashimoto and Raynaud diseases) associations were detected.

**Conclusion:** Our study demonstrated an absence of clear association between HPV vaccines and autoimmune and other rare diseases. The review also highlights the need for more systematic collaborations to monitor rare safety adverse events.

**Key Words:** papillomavirus vaccines, autoimmune diseases, rare adverse events, postlicensure studies

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Human papillomavirus (HPV) vaccines are effective in reducing HPV infections<sup>1,2</sup> and in preventing cervical cancer, caused by certain HPV genotypes.<sup>3</sup> Currently 3 licensed HPV vaccines are available: a quadrivalent HPV vaccine (4vHPV; Gardasil, Merck, USA) and a bivalent HPV vaccine (2vHPV; Cervarix, GSK, Belgium) licensed in 2006 and 2007, respectively, followed in late 2014 by 9-valent HPV vaccine (9vHPV; Gardasil9, Merck, USA). Table 1 summarizes the characteristics of the 3 vaccines. All 3 HPV vaccines were initially licensed and marketed using a 3-dose vaccination schedule. However, a 2-dose schedule was subsequently approved for all 3 vaccines. HPV vaccines are available in more than 100 countries,<sup>4</sup> and over 80 countries have included the HPV vaccine into their national immunization programs mainly targeting young adolescent girls.<sup>5</sup> As of 2014, it is estimated that 59 million women have received at least 1 dose of HPV vaccine.<sup>6</sup> Routine vaccination of boys is currently implemented in several countries worldwide.

To enhance the immune response, HPV vaccines contain adjuvanted systems, such as toll-like receptors or oil-based emulsions. These adjuvant vaccines enhance a general immune response and may potentially trigger autoimmune reactions (responses against body's own tissue).<sup>7</sup> The safety of vaccines and its adjuvants require assessment pre licensure and continuous monitoring post licensure. This is done by passive surveillance of case reports and active surveillance studies, aiming to detect rare reactions or associations with diseases that have low incidences. As part of postmarketing commitments and requests, several studies were conducted aiming to estimate the risks of developing autoimmune diseases following HPV vaccination.<sup>8,9</sup> To date, available meta-analysis of HPV vaccine and autoimmune diseases have largely synthesized results of clinical trials<sup>10</sup> or a mix of postlicensure studies and clinical trials.<sup>11</sup> To address the need to analyze available postlicensure safety data, we carried out a systematic review of postlicensure observational safety studies assessing the risk of autoimmune and rare adverse events following HPV vaccination; we describe the methodologic approaches used and we summarize the risk estimates.

## MATERIALS AND METHODS

We used a comprehensive 3-step search strategy to identify relevant studies. No language restrictions were placed on the searches or search results. The study conforms to the Preferred Reporting Items for Systematic reviews and Meta-analysis guidelines<sup>12</sup> and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance<sup>13</sup> (ENCePP) guidelines.

## Search Strategy and Selection Criteria

First, we searched Embase.com, Medline (Ovid), ISI Web of Science and Cochrane Central from inception to April 16, 2019, for any postlicensure observational safety studies assessing the risk of autoimmune adverse events following HPV vaccination. A search strategy was developed for each database with a combination of free

**TABLE 1.** Characteristics of HPV Vaccines

	Cervarix (Recombinant, Adjuvanted, Adsorbed)	Gardasil (Recombinant, Adsorbed)	Gardasil9 (Recombinant, Adsorbed)
Recommended route of administration	Intramuscular Suspension	Intramuscular Suspension	Intramuscular Suspension
Characteristics by dose (0.5 mL)	L1 virus-like particle types HPV-16 (20 µg), 18 (20 µg)	HPV-6 (20 µg), 11 (40 µg), 16 (40 µg), 18 (20 µg)	HPV-6 (30 µg), 11 (40 µg), 16 (60 µg), 18 (40 µg), 31 (20 µg), 33 (20 µg), 45 (20 µg), 52 (20 µg), 58 (20 µg)
Cross-protection Adjuvant	HPV-31, HPV-33, HPV-45 Adsorbed on aluminum hydroxide, hydrated (Al(OH) <sub>3</sub> ) (0.5 mg) Al <sub>3</sub> <sup>+</sup> in total Adjuvanted by AS04 containing: 3--desacyl-4'-MPL (50 µg)	HPV-31 Adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant (0.225 mg Al)	None Adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant (0.5 mg Al)
Expression system	Baculovirus-insect cell	Yeast cells	Yeast cells

MPL, monophosphoryl lipid A.

text and controlled vocabulary (ie, medical subject headings terms). Additional search terms were included in consultation with a reference librarian (WB). The detailed search strategies for each database are presented in Table, Supplemental Digital Content 1, <http://links.lww.com/INF/D738>. Second, we screened reference lists of publications retrieved to identify additional relevant studies. Third, we searched web-based platforms including the EnCePP register<sup>14</sup> and manual searches in health authorities' websites and Google Scholar.

Two reviewers (CW, KG) independently screened titles and abstracts followed by the retrieval and reviewed full-text articles according to the predefined eligibility criteria described below. Disagreements were resolved through discussion. The following inclusion criteria were applied: (1) HPV vaccination; (2) postlicensure studies; (3) epidemiologic or Phase IV studies; (4) healthy population and (5) risk/safety assessment. Commentaries, meeting reports, letters to editors, case reports, biologic or animal studies were excluded. Eligible papers, as well as papers which could not be excluded right away, were then included in the full-text assessment. Selected papers were assessed by reviewing the full-text according to the following inclusion criteria: (1) HPV-related adverse events, (2) autoimmune diseases and rare safety outcomes assessment, (3) no assessment using spontaneous reporting database.

### Data Abstraction and Quality Assessment

For each of the eligible studies, we extracted the following data as a minimum: first author and year of publication, study design, objective and period, data source, geographical area, age of subjects, type of vaccine, adverse events reported either as individual or composite endpoints, method for identification and validation of cases, disease onset, risk window and risk estimates.

The study quality was assessed by the 2 same reviewers using an adapted quality checklist combining the Newcastle–Ottawa Scale<sup>15</sup> and the Scottish Intercollegiate Guidelines Network<sup>16</sup> quality criteria for cohort and case-control studies. The adapted quality checklist, including assessment of case-only design, is presented in Table, Supplemental Digital Content 2, <http://links.lww.com/INF/D739>. To assess the quality of the studies, we scored each of the studies following 4 parameters: the selection of study groups (2 points), confounding factors (1 point), assessment of the outcome (3 points) and assessment of the exposure (1 point). The total score represented the sum of scores for each parameter. This score was used as a relative measure of data quality; no threshold for exclusion was applied.

### Data Analysis

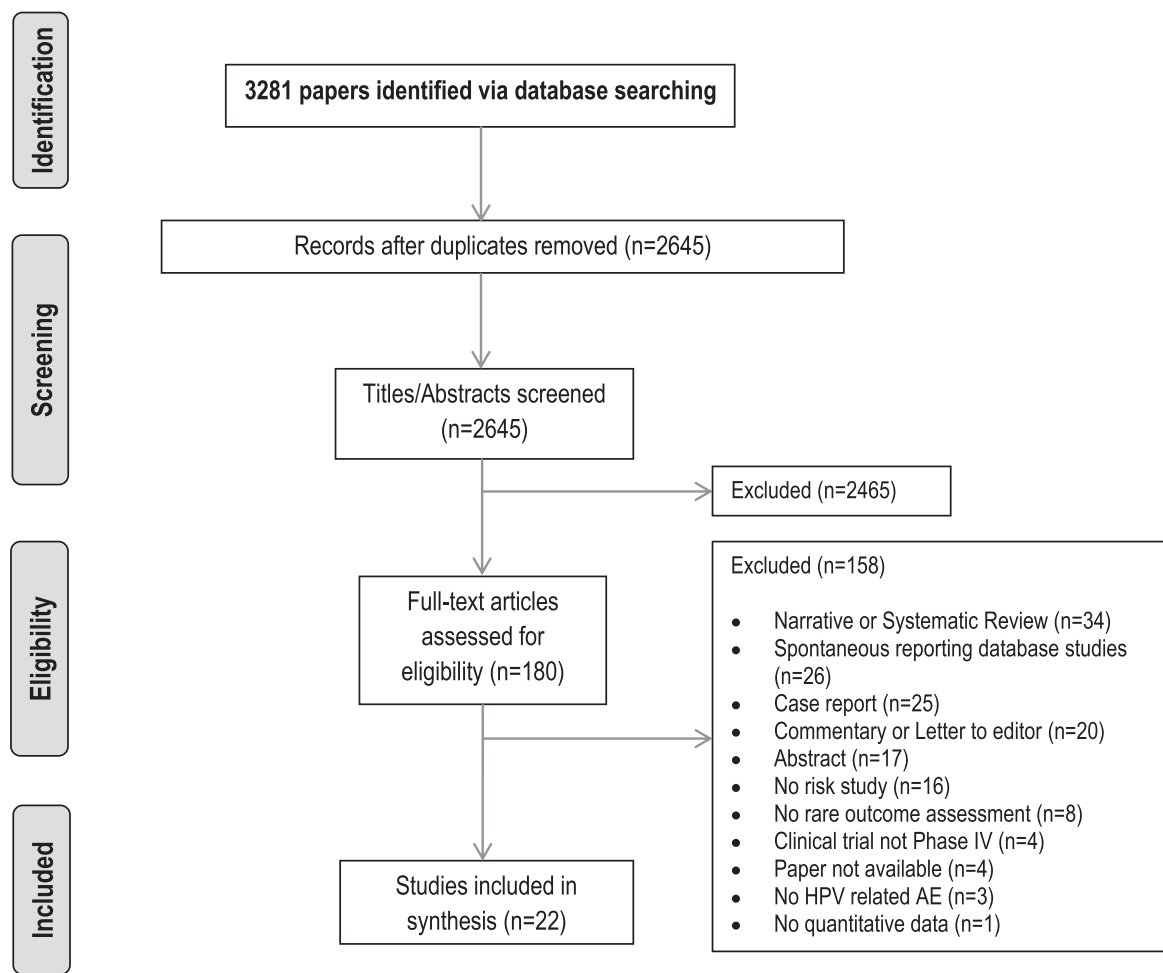
Pooled risk estimates (odds ratios, ORs) and their respective 95% confidence intervals (CIs) for individual autoimmune diseases

were calculated if at least 2 risk estimates per outcome and per HPV vaccine type were available. Under the rare disease assumption, the OR and relative risk (RR) can be treated as approximately equal. Therefore, the pooled estimate was computed by pooling any risk estimates, independently of the type of risk measurement (relative risk, OR or hazard ratio) and by using fixed-effects model (Mantel-Haenszel method) or random-effects model (Der Simonian-Laird method). To determine the extent of variation between studies, we computed heterogeneity tests with Higgins  $I^2$  statistic to measure the proportion of observed variance that reflects true effect sizes.  $I^2$  values over 50% were considered as relevant inconsistency between studies. Statistical analyses were performed using Stata software.<sup>17</sup>

## RESULTS

Of the 3281 papers, 180 potentially relevant full-text articles were independently reviewed. From these, 22 studies (<1%) were identified as relevant for our review. Figure 1 depicts the Preferred Reporting Items for Systematic reviews and Meta-analysis flowchart. Consultation of the ENCePP register and other websites did not identify additional studies of interest.

Table, Supplemental Digital Content 3, <http://links.lww.com/INF/D740> shows the main characteristics of the 22 postlicensure observational studies meeting the inclusion criteria. Studies were published from 2012 to 2019. Fourteen studies were conducted in Europe [Denmark and Sweden (5), Finland (1), France (3), Norway (1), the Netherlands (1) and UK (3)] and 8 in North America [Canada (2) and USA (6)]. Most studies used a retrospective study design and a variety of types of data sources: registers in Nordic countries, general practitioners and hospital databases in UK and Canada, and claims databases in France and USA. Two prospective studies were conducted in France by using the Pharmacoepidemiologic General Research Extension methodology, a research platform recruiting prospectively and routinely autoimmune disorder cases through a network of specialists. Most studies included females only with ages ranging from 9 to 44 years, 1 study included males only, and 2 studies included males and females of any age. Various types of study designs were implemented to assess the risk of autoimmune diseases after HPV vaccination; 3 case-control studies including 1 matched,<sup>18</sup> 1 unmatched<sup>19</sup> and 1 nested case-control<sup>20</sup>; 7 case-only designs including 5 self-controlled case series<sup>21–25</sup> and 2 case-centered method<sup>26,27</sup>; and 12 cohort studies<sup>8,9,28–37</sup> including a surveillance study.<sup>8</sup> More than 60 different autoimmune and rare adverse events were studied. Some studies focused on any autoimmune diseases (n = 4),<sup>8,9,18–27,29,30,33,34,36,37</sup> others (n = 18)<sup>8,9,18–27,29,30,33,34,36,37</sup> targeted specific outcomes. Type 1 diabetes mellitus was the most frequently studied (in 11 studies).<sup>8,9,18,19,24,28,31–33,35,37</sup> Autoimmune



HPV = Human Papillomavirus Vaccine, AE = Adverse Event

**FIGURE 1.** PRISMA flowchart of the selection procedure. PRISMA indicates Preferred Reporting Items for Systematic reviews and Meta-analysis.

thyroiditis diseases<sup>8,9,19,24,28,32,35,37</sup> including Hashimoto and Grave diseases, hypothyroidism and other hyperthyroidism, and immune thrombocytopenia purpura<sup>8,9,18,19,24,28,32,35</sup> (ITP) were assessed in 8 studies: Crohn disease<sup>21,24,28,32,35,37</sup> in 6 studies, Bell palsy,<sup>24,28,31,32,35</sup> coeliac disease,<sup>9,28,31,32,35</sup> juvenile rheumatoid arthritis,<sup>8,9,24,35</sup> optic neuritis,<sup>8,24,27,28,36</sup> rheumatoid arthritis,<sup>8,9,28,31,32</sup> ulcerative colitis<sup>24,28,31,32,35</sup> and systemic lupus erythematosus<sup>8,9,28,32,35</sup> in 5 studies; acute disseminated encephalomyelitis,<sup>8,20,24,26</sup> chronic fatigue syndrome,<sup>22,25,30,35</sup> epilepsy,<sup>28,31,32,35</sup> Henoch–Schonlein purpura,<sup>28,31,32,35</sup> pancreatitis,<sup>9,28,32,35</sup> paralysis,<sup>28,31,32,35</sup> psoriasis,<sup>28,31,32,35</sup> vasculitis,<sup>9,28,31,32</sup> venous thrombocytopenia<sup>23,28,31,35</sup> and vitiligo<sup>28,31,32,35</sup> in 4 studies; ankylosing spondylitis,<sup>28,31,32</sup> erythema nodosum,<sup>28,32,35</sup> hemolytic anemia,<sup>8,24,32</sup> multiple sclerosis,<sup>8,20,34</sup> myositis,<sup>28,32,35</sup> narcolepsy,<sup>28,31,32</sup> Raynaud disease,<sup>28,32,35</sup> scleroderma<sup>9,28,32</sup> in 3 studies. Four studies<sup>9,19,21,29</sup> among 7 including data on Guillain-Barre syndrome (GBS) provided risk estimates. Fourteen studies<sup>8,18,20,23,24,26–32,34,36</sup> concerned 4vHPV vaccine exposure, while 4 studies<sup>22,25,35,37</sup> assessed 2vHPV vaccine exposure. Two studies<sup>9,21</sup> provided risk estimates separately for 4vHPV and 2vHPV vaccine exposures. Two studies<sup>19,33</sup> assessed a combined exposure to both 2v- and 4vHPV and both 4vHPV and 9vHPV vaccines.

Based on the adapted quality checklist, the 22 studies included in this review were considered to have a satisfactory

methodologic quality. The quality assessment scores for each study are reported in Table, Supplemental Digital Content 3, <http://links.lww.com/INF/D740>.

### Methodologic Approaches

Methodologic considerations of the 22 studies including methods for identification and validation of cases, diagnostic criteria, onset of the diseases and analytical parameters are further detailed in Table, Supplemental Digital Content 4, <http://links.lww.com/INF/D741>.

### Definition of Outcome

Five studies<sup>8,9,20,27,37</sup> developed complex algorithms combining diagnosis codes and additional clinical information such as medications, laboratory test results and referral to specialists to identify cases. Fifteen studies<sup>19,21–26,28–36</sup> identifying cases by diagnosis codes only implemented a review of all medical charts or contacted health-care providers (6 studies).<sup>21,24,26,27,33,36</sup> Three studies,<sup>8,20,37</sup> in addition to elaborated algorithms, put in place a case ascertainment process with a panel of specialist physicians. In most of the studies, the disease onset was the date of the first diagnosis, whereas in 2 studies<sup>20,37</sup> using case ascertainment process, the criteria of first clinical sign or symptom were used.

## Analytical Parameters

In some studies,<sup>18,19,24,34,37</sup> the researchers created composite endpoints including multiple disease conditions such as for demyelinating diseases, connective tissue disorders or neuroinflammatory diseases. Two studies<sup>24,37</sup> analyzed composite endpoints as primary objective, while all other studies assessed individual endpoint as their primary objective. Several time frames, most often disease-specific, were evaluated in case-control designs ranging from 14 days until 3 years before disease onset. In cohort designs, the follow-up time varied from 180 days until 10 years after the last exposure irrespective of the disease. Case-only study designs were usually applied for individual endpoints only. In those studies, risk windows were defined according to the disease varying from 42 days to 1 year after disease onset. Detailed risk windows are presented in Table, Supplemental Digital Content 4, <http://links.lww.com/INF/D741>.

## Risk Estimates

We computed pooled risk estimates for the following categories of autoimmune diseases: dermatologic (including erythema nodosum, psoriasis, scleroderma, systemic lupus erythematosus and vitiligo); hematologic (including ITP); gastrointestinal (including coeliac, Crohn disease, pancreatitis and ulcerative colitis); musculoskeletal or systemic diseases (including ankylosing spondylitis, Henoch-Schönlein purpura, juvenile rheumatoid arthritis, myositis, rheumatoid arthritis and vasculitis); neurologic (Bell palsy, epilepsy, GBS, chronic fatigue syndrome, narcolepsy and paralysis); ophthalmic (optic neuritis); other demyelinating diseases (including central nervous system disorders and multiple sclerosis); thyroiditis disorders (including Hashimoto, Graves' disease and other hyperthyroidism); other disorders (including Raynaud disease, Sjögren syndrome and venous thrombocytopenia) and type 1 diabetes. Pooled estimates were computed for 35 disease conditions corresponding to 48 pooled estimates. Pooled estimates are reported in Table 2. Risk estimates for all autoimmune diseases and other rare events are reported in Table, Supplemental Digital Content 5, <http://links.lww.com/INF/D742>. Most of them were computed for 4vHPV ( $n = 34$ ) and the remaining for 2vHPV ( $n = 14$ ). Majority of the pooled estimates did not show significant association ( $n = 43$ ). Three pooled estimates showed a protective effect for ITP [OR = 0.55 (95% CI: 0.34–0.88)] and chronic fatigue syndrome [OR = 0.77 (95% CI: 0.62–0.97)] after 2vHPV vaccine and for paralysis [OR = 0.52 (95% CI: 0.55–0.77)] after 4vHPV vaccine. Two pooled estimates showed a statistically significant increased risk for Hashimoto disease [OR = 1.25 (95% CI: 1.09–1.44)] and Raynaud disease [OR = 1.63 (95% CI: 1.21–2.20)] after 4vHPV vaccine.

For diseases reported in a single study, 9 risk estimates showed statistically significant associations (Table, Supplemental Digital Content 5, <http://links.lww.com/INF/D742>). Increased risks with relatively large 95% CI were observed in males following 9vHPV for narcolepsy [RR = 3.44 (95% CI: 1.08–11.0)] and vitiligo [RR = 4.70 (95% CI: 1.13–19.5)].

## DISCUSSION AND CONCLUSIONS

Following large-scale use of HPV vaccines, rare serious adverse events have been reported which prompted additional investigations.<sup>38–40</sup> Further to this, several postlicensure studies were conducted to estimate associations between HPV vaccination and autoimmune and other rare adverse events. The present review is to our knowledge the first comprehensive review aiming to describe the methodologic approaches used in HPV vaccine postlicensure observational studies. In addition, we aimed to summarize risk estimates of autoimmune and other rare events following immunization with HPV from the available evidence. Among

the 22 postlicensure observational safety studies included, we identified 2 important elements informing on the validity and robustness of postlicensure studies assessing rare adverse events.

The first element is related to the validity of the clinical outcomes and determination of onset of disease. In the eligible studies, simple to more complex algorithms were developed to identify and validate cases of autoimmune diseases. The level of granularity of the clinical case definition may generate, if not consistent across studies, an important source of heterogeneity restricting direct comparison between studies. As an example, 1 study<sup>9</sup> broadly defined autoimmune thyroiditis diseases including in its definition codes for disease of nonautoimmune origin, while other studies<sup>8,24,28,32,35</sup> targeted specific medical conditions such as Hashimoto disease. In addition, algorithm-based approach should ensure a high specificity of the outcome definition and therefore avoid inclusion of false-positive subjects. Algorithm-based search only is deemed sufficiently robust to detect acute events such as GBS. However, for diseases with insidious onset, such approach may introduce bias on the true onset date.

Second important element is related to the analytical parameters including risk period, endpoints and sample size. While a long and sufficient follow-up time is required for long latency diseases to be detected, risk period must be adequately defined to establish accurate evidence of a causal relationship. Some autoimmune events are known to occur within few weeks after vaccine exposure such as GBS detected between 6 and 8 weeks after swine flu vaccine.<sup>41,42</sup> For some other autoimmune diseases, evidence of time to disease onset (ie, multiple sclerosis)<sup>43</sup> or lag time between onset of symptoms and disease diagnosis (ie, rheumatoid arthritis)<sup>44</sup> are not well clearly established. In such circumstances, risk periods should be defined as much as possible using epidemiologic and mechanistic evidences or by expert opinion. Sensitivity analyses using different risk periods and clustering analyses are complementary methods to highlight potential windows of risk. A disease-specific time frame should be the preferred approach when different kind of clinical events are under assessment. In case-only study design, a washout period between risk and control periods should also be preferably considered, to avoid misclassification.<sup>45</sup> In the studies, sample sizes limitations were overcome by creating composite endpoints or by combining multiple healthcare databases. With intrinsic limitations such as heterogeneity between databases or lack of specificity of the outcome of interest, both alternative approaches emphasize the need for collaboration to increase sample size and develop common clinical definitions. Because of the rarity of autoimmune diseases, some of the studies included in our review may not be adequately powered to detect a potential increased or decreased risk. This possible lack of statistical power may suggest an unreliable absence of risk. In addition, 2vHPV vaccine was less frequently studied and therefore no estimation of risk could be generated for some of the diseases.

Our review also provides pooled risk estimates. Pooled findings in females suggested that 4vHPV vaccination significantly increased the risk of both Hashimoto and Raynaud diseases. The slightly elevated risk of Hashimoto disease was mainly driven by the Chao et al<sup>8</sup> study. After further evaluation, the researchers demonstrated that most of the new onset cases were likely preexisting cases and that no consistent evidence for a safety signal for autoimmune thyroid conditions in general was observed among vaccinated subjects. Similarly, the increased risk of Raynaud disease was driven by the Arnheim-Dahlström et al<sup>28</sup> study. The researchers discriminated this safety signal based on prespecified causality criteria including the strength of the association (rate ratio < 3.0). On the contrary, a protective effect was observed for paralysis after 4vHPV and for ITP and chronic fatigue syndrome after 2vHPV. By

**TABLE 2.** Summary of Pooled Estimates (ORs) for 35 Autoimmune Diseases and/or Other Rare Adverse Events

Outcomes	HPV Vaccine Exposure	Pooled Estimates* [OR (95% CI)]	I <sup>2</sup> Statistics (%)
<b>Dermatologic</b>			
Erythema nodosum	4vHPV	1.26 (0.89; 1.79)	0.0
Psoriasis	4vHPV	1.03 (0.87; 1.23)	0.0
Scleroderma	4vHPV	1.04 (0.64; 1.69)	29.7
Systemic lupus erythematosus	4vHPV	1.04 (0.82; 1.33)	0.0
	2vHPV	1.20 (0.39; 3.68)	20.5
Vitiligo	4vHPV	1.31 (0.91; 1.87)	25.6
<b>Diabetes</b>			
Diabetes type 1 diabetes mellitus	4vHPV	0.93 (0.65; 1.34)	86.5
	2vHPV	0.80 (0.50; 1.26)	58.5
<b>Hematologic</b>			
Idiopathic thrombocytopenia purpura	4vHPV	1.06 (0.85; 1.33)	40.2
	2vHPV	<b>0.55 (0.34; 0.88)</b>	0.0
<b>Gastrointestinal</b>			
Coeliac disease	4vHPV	1.16 (0.87; 1.56)	67.3
	2vHPV	1.05 (0.80; 1.38)	0.0
Crohn disease	4vHPV	1.04 (0.73; 1.47)	69.3
	2vHPV	1.17 (0.77; 1.78)	0.0
Pancreatitis	4vHPV	0.87 (0.69; 1.08)	0.0
	2vHPV	1.68 (0.85; 3.33)	0.0
Ulcerative colitis	4vHPV	0.93 (0.58; 1.50)	80.7
	2vHPV	0.57 (0.15; 2.23)	80.7
<b>Musculoskeletal/systemic</b>			
Ankylosing spondylitis	4vHPV	0.98 (0.65; 1.48)	0.0
Behcet syndrome	4vHPV	1.52 (0.29; 7.96)	69.4
Henoch–Schonlein purpura	4vHPV	1.03 (0.66; 1.60)	0.0
Juvenile rheumatoid arthritis	4vHPV	0.73 (0.36; 1.47)	77.7
	2vHPV	1.03 (0.82; 1.29)	6.2
Myositis	4vHPV	0.92 (0.50; 1.69)	0.0
Polymyositis/dermatomyositis	4vHPV	0.83 (0.46; 1.51)	0.0
Rheumatoid arthritis	4vHPV	0.92 (0.72; 1.17)	0.0
Vasculitis	4vHPV	1.11 (0.86; 1.42)	0.0
<b>Neurologic</b>			
Bell palsy	4vHPV	0.79 (0.46; 1.35)	73.8
	2vHPV	1.37 (0.83; 2.26)	0.0
Epilepsy	4vHPV	0.81 (0.54; 1.24)	87.7
Guillain-Barre syndrome	4vHPV	1.79 (0.65; 4.94)	64.0
	2vHPV	2.89 (0.58; 14.40)	69.7
Chronic fatigue syndrome	2vHPV	<b>0.77 (0.62; 0.97)</b>	11.5
Narcolepsy	4vHPV	1.08 (0.64; 1.84)	19.3
Paralysis	4vHPV	<b>0.52 (0.35; 0.77)</b>	0.0
<b>Ophthalmic</b>			
Optic neuritis	4vHPV	1.20 (0.84; 1.71)	19.8
<b>Other demyelinating diseases</b>			
Central nervous system demyelinating syndrome	4vHPV	1.02 (0.77; 1.33)	0.0
Multiple sclerosis	4vHPV	0.96 (0.77; 1.21)	0.0
<b>Other disorders</b>			
Raynaud disease	4vHPV	<b>1.63 (1.21; 2.20)</b>	0.0
Sjogren syndrome	4vHPV	1.34 (0.71; 2.51)	0.0
Venous thrombocytopenia	4vHPV	0.80 (0.60; 1.07)	0.0
<b>Thyroid</b>			
Hashimoto disease	4vHPV	<b>1.25 (1.09; 1.44)</b>	0.0
	2vHPV	0.88 (0.57; 1.36)	0.0
Grave disease	4vHPV	0.88 (0.73; 1.07)	3.7
	2vHPV	1.12 (0.56; 2.24)	63.3
Autoimmune thyroiditis	4vHPV	1.10 (0.94; 1.27)	0.0
	2vHPV	1.76 (0.65; 4.77)	83.3
Other hyperthyroidism	4vHPV	0.98 (0.79; 1.22)	0.0

Bold estimates are statistically significant.\*Pooled estimates were computed using fixed-effects model or random-effects model (I<sup>2</sup> > 50%) in Stata v14.0.

using criteria such as the strength of the association, the consistency of the reported risks and the level of significance to interpret the risk estimates, we noticed a lack of clear association for all protective and risk effects with regard to HPV vaccines. In addition, the pooled analysis has several limitations due to heterogeneity of

clinical definitions, targeted age categories and variation in risk periods across studies. Two studies<sup>28,32</sup> conducted in Sweden and Denmark used same sources of data but targeted 2 different age categories (10–17 and 18–44 years old). Therefore, the pooled estimate for Raynaud disease and paralysis does not bring any added

value and only the individual studies can confirm the observed risks. Similarly, a higher risk of Hashimoto disease was observed from a pool of 3 studies for which the age of the populations did not necessarily overlap. Moreover, the small number of studies included in our analysis did not allow stratification by type of study design or risk estimates. The pooling of any risk estimates did not affect drastically the pooled estimates because for rare events OR and relative risk are virtually similar. However, while each individual study was fit-for-purpose for the stated objectives, the variability of methods across studies may impact the ability to validly characterize risks. The risk evaluation in our review should be considered as an indicator of possible harms after HPV vaccination for which enhanced and continuous surveillance should be maintained or implemented. A recently published meta-analysis<sup>11</sup> also showed a small increased risk of Hashimoto disease after HPV vaccination. However, the authors did not provide analysis by type of HPV vaccine. Because the mechanisms of action of adjuvant systems may perform differently, a critical evaluation by type of vaccine may help to discriminate any potential triggering effect.

This review also underlines the need for harmonization of outcome definitions and collaboration in assessing vaccine safety, which is one of the efforts currently done in the ADVANCE project<sup>46</sup> in the European Union and was possible globally for assessing safety of the pandemic influenza vaccine.<sup>47</sup>

In conclusion, this systematic review emphasizes the diversity of methodologic approaches to assess the risk of developing rare adverse events after HPV vaccination. Results show that many events have been studied but not systematically for the different HPV vaccines. The review highlights that positive and negative associations were observed with autoimmune diseases. However, these estimates should be interpreted with caution due to the diversity in methodologic approaches used by the studies included in this review. More systematic collaborations and harmonization of event clinical definitions are needed to monitor rare safety events.

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