ORIGINAL ARTICLE

HPV vaccine and autoimmune diseases: systematic review and meta-analysis of the literature

C. GENOVESE[1], V. LA FAUCI[1], A. SQUERI[1], G. TRIMARCHI[2], R. SQUERI[1]
[1] Department of Biomedical Sciences and Morphological and Functional Images, University of Messina, Postgraduate Medical School in Hygiene and Preventive Medicine, Messina, Italy; [2] Department of Economics, University of Messina, Italy

Keywords

Sistematic review • Meta-analysis • HPV vaccine • Autoimmune diseases

Summary

Background. *In the literature conflicting opinions are detectable on the onset of adverse events as autoimmune disease post HPV vaccine and often case reports describes the onset of one of these events, but don't emerge a clear relationship and we don't have data to support it.*
Methods. *We carried out a systematic review to identify all scientific publications dealing with the correlation between vaccine anti-papillomavirus and new onset of autoimmune diseases. We searched the main scientific databases (PubMed, Sciverse Scopus, Web of knowledge and Cochrane Central Register of Controlled Clinical Trials) for the following search terms: "vaccine"; "anti-papillomavirus"; "autoimmune"; "disease"; "disorder". To evaluate the safety of HPV vaccines, the dichotomous data on the number of subjects experiencing an autoimmune disorder in the study vaccine group and the placebo group were extracted from each study with subsequent determination of the risk ratios and their 95% confidence intervals. We combined data statistically using a random effects model.*
Results. *We conduct a meta-analysis on six studies on bivalent and quadrivalent HPV vaccine. The total number of subjects included in the meta-analysis comprised 243,289 in the vaccine group and 248,820 in control groups. Four of the six trials had a Jadad score of 3 or 4 indicating an adequate trial quality. The most frequent autoimmune disease observed across the six studies were musculoskeletal,CNS conditions and endocrinological conditions . The results of the meta-analysis demonstrated no correlation between autoimmune disorders and HPV vaccines (pooled OR 1.038, 95% CI 0.689-1.562).*
Conclusions. *No correlation was identified for bivalent and quadrivalent HPV vaccines. It's therefore essential to correctly inform the general population in order to try to increase both Italian and international vaccination coverage.*

Introduction

Human papillomavirus (HPV) is one of the commonest sexually transmitted viruses worldwide, with initial infections typically occurring soon after sexual debut. Today more than 290 million women have a human papillomavirus (HPV) infection. An effective vaccine is available as part of routine immunization programmes in 65 countries. In low- and middle-income countries, where most cases of cervical cancer occur, if 70% vaccination coverage were achieved the deaths of more than 4 million women would be avoidedover the next decade [1].
There are three vaccines currently available: one bivalent that protects against HPV types 6 and 11 which are the most common causes of genital warts,one quadrivalent, which also provides protection against HPV types 16 and 18 and the last one nonavalent vaccine that contains serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58.. Despite this availability, the latest HPV vaccination coverage in USA estimates show that only 60 percent of adolescents aged 13-17 years have received one or more doses of HPV vaccine, with a gender gap in HPV vaccination rates (about 65 percent of females having received the first dose of HPV vaccine compared to 56 percent for males) and only 43 percent of adolescents are up to date with all recommended doses of HPV vaccine [2].
The most common reasons given for refusing the HPV vaccine were lack of vaccine endorsement by physicians, lack of perceived need for the vaccine, lack of knowledge and safety concerns and caregivers' concerns about safety or potential side effects [3-6].
One of the frequently attributed effects to the HPV vaccine that is cited in the literature is the onset of autoimmune disease. Alleged associations between HPV vaccinations and autoimmune disorders (ADs) have been reported in the international literature and the most frequently proposed mechanism to account for these is molecular mimicry [7-11].
Objectives: in this study, we want to investigated whether the HPV vaccine is associated with the onset of ADs.

Materials and methods

Search strategy and selection criteria

We carried out a systematic review to identify all case control study dealing with the correlation between vaccine anti-papillomavirus and new onset of autoimmune diseases.
This is "a condition in which the body recognizes its own tissues as foreign and directs an immune response

against them" such as gastroenteritis, connective tissue disorders, alopecia, CNS conditions and endocrine autoimmune disease, etc… We searched the main scientific databases (PubMed, Sciverse Scopus, Web of knowledge and Cochrane Central Register of Controlled Clinical Trials for the following search terms: "vaccine"; "anti-papillomavirus"; "autoimmune"; "disease"; "disorder", using the function "AND" and "OR". The bibliographies of all relevant articles, including reviews, were screened for further references. No language restrictions were imposed; papers in languages we were unable to read were translated using Google Translate. We developed the search terms in accordance with the Medical Subject Headings thesaurus, using a combination of test searches and via collaboration between independent researchers and knowledge users. After deleting duplicates, we further screened titles, abstracts, or entire articles using exclusion criteria. Screening was carried out independently by two authors (RS, CG). Any disagreement about eligibility between reviewers was resolved by a third author (VLF). The first two authors extracted data from included papers using a data extraction form reviewed by the other co-authors. These procedures comply with the PRISMA guidelines for reporting systematic reviews [12].

Data extraction

Two independent reviewers (CG and RS) identified potentially relevant articles and collected the following data: first author's last name; year of publication; clinicaltrials.govidentifier (if applicable); study design; total number of participants; age range; gender; disease background and study arms with number of vaccinated participants in each arm. We found after this process only clinical trial for the purpose of our study,

Evaluation of study quality

AD outcomes were identified from the included studies and considered for the meta-analysis. We used the Cochrane guidelines for systematic reviews of interventions [13] and two reviewers (CG, RS) independently assessed the quality of individual studies included in the meta-analysis. The Jadad scale for reporting randomised controlled trials (RCTs) was employed. This assigns an overall score of the methodological quality of a study from zero to five [14]. Although studies were not on the basis of this assessment, the quality scores were taken into account when describing results.

Data analysis

To evaluate the safety of HPV vaccines, the dichotomous data on the number of subjects experiencing an AD in the study vaccine group and the placebo group were extracted from each study with subsequent determination of the risk ratios (RR) and their 95% confidence intervals (CI). We combined data statistically using a random effects model. I2 statistics and test Q di Cochran were used to assess the heterogeneity between the studies included. Values of I2 can be interpreted as low (25-50%), moderate (50-75%), and high (75% and higher) levels of heterogeneity. Meta-analyses were performed using package "meta" rel.4.9 of the software R.

Dealing with missing data

Our analysis relies solely on existing data.

Assessment of reporting biases

Due to the limited number of studies available for meta-analysis, assessment of publication bias was not applicable. The review is subject to publication bias.

Results

A total of 235 references were identified from electronic databases in the search performed on May 3 and 4, 2018 (Fig. 1). Once duplicate entries (116) had been removed, references were further evaluated for inclusion based on the title and/or abstract. 119 potentially relevant articles were thereby included in the next stage for full-text evaluation. These publications included: 3 reviews, 8 animal studies,14 case reports, and 2 were studies regarding treatments; the other studies were position papers, letters comments and replies. The characteristics of the study population, interventions, control groups, the evaluated outcomes and/or design of the study (PICOS) failed to meet the inclusion criteria in 113 publications. Most of these studies were excluded as they did not include a control group. Ultimately, a total of six RCTs fulfilled all inclusion criteria and were selected for the meta-analysis [17-20].

Study characteristics

The main characteristics of the selected RCTs are summarized in Table I.

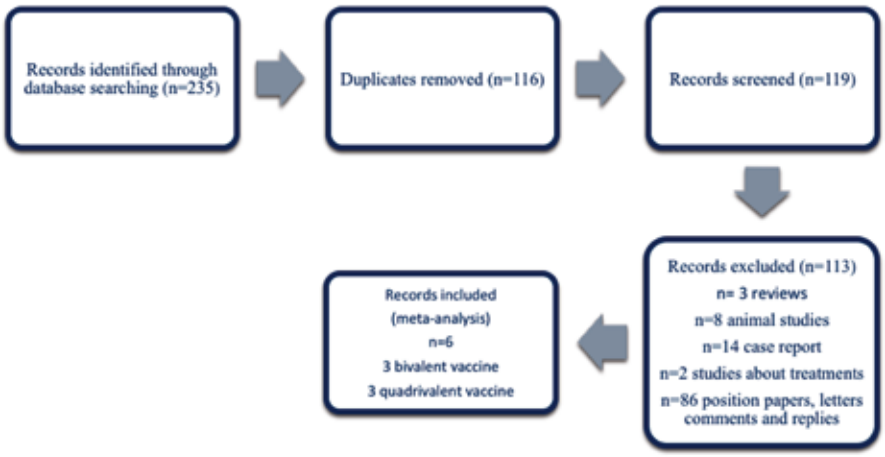
Of the six studies selected, three used a bivalent vaccine and three a quadrivalent vaccine. The six vaccine trials on enrolled a total of 492,109 individuals, 243,289 in the treatment group (i.e. subjects administered vaccines) and 248,820 in the control groups (i.e. subjects receiving another vaccine (such as HBV vaccine, HA vaccine)or no vaccine). The age of the enrolled subjects in the nine studies varied from 9 to 26 years and all studies reported the number of subjects who experienced a specific AD.

In the study by Geier et al. the vaccine adverse event reporting system (VAERS) database was examined for adverse event reports associated with vaccines administered from January 2006 through December 2012 to recipients between 18 and 39 years old with a listed residence in the USA and a specified female gender [15].

In the study by Block et al. females aged 9 to 26 years and males aged 9 to 16 years received at least 1 dose of HPV-6/11/16/18 vaccine or placebo and were studied for all serious and nonserious adverse events (AEFI) s and any new medical conditions were also recorded for the entire study period [18].

In the study by Verstraeten et al. AEFI data were collected prospectively. In addition to a study-specific list of local or general events solicited during a brief period following vaccination, unsolicited AEFI were cat-

Fig. 1. Flowchart of the evaluation and inclusion process for the meta-analysis [21].



Tab. I. Characteristics of the included studies.

Authors, year	Enrollment	Age range (yrs)	Study arms 1	Study arms 2
Geier, 2015	22,011	9-26	5124	16887
Verstraetena, 2008	68,512	> 10	36,744	31,768
Block, 2010	21,464	9-26	11,778	9,686
Grimaldi-Bensouda, 2014	1,365	14-26	269	1,096
Angelo, 2014	47,857	9-25	27,353	20,504
Willame, 2016	129,937	> 9	64,964	64,973

egorized as follows: non-serious AEFI, serious AEFI, medically significant events and new onset of chronic disease. These were reported to investigators during a study visit and were collected for 30 days after each vaccine dose [16].

In the study by Grimaldi-Bensouda a total of 113 specialized centers recruited (from December 2007 to April 2011) females aged 14-26 years with incident cases of six types of ADs: idiopathic thrombocytopenic purpura (ITP), central demyelination/multiple sclerosis (MS), Guillain-Barrè syndrome, connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis/juvenile arthritis), type 1 diabetes mellitus and autoimmune thyroiditis. Control subjects matched to cases were recruited from general practice. Cases and controls were compared with regard to exposure to the quadrivalent HPV vaccine [17].

In the study by Willame et al. 9-25 year-old women after the first AS04-HPV-16/18 vaccine dose were compared to three unexposed cohorts and were observed within the one year follow-up period [20]. In the study by Angelo et al. three groups were considered: adolescent girls/women receiving HPV-16/18-vaccine alone (HPV group), subjects receiving HPV-16/18-vaccine coadministered with another vaccine and subjects receiving no vaccine (HVP group control) and unsolicited AEFI were reported for 30 days after each dose [19].

Study quality

The methodological quality of the included RCTs was satisfactory (Tab. I), except for those conducted by Geier and Verstraeten et al. Four out of the six studies (66.6%) had a score of 3 or 4 on the Jadad scale. The studies by Geier and Verstraeten et al scored 0 as no information was available about randomized method and blinding of these studies.

These publications included: 3 reviews, 8 animal studies,14 case reports, and 2 were studies regarding treatments; the other studies were position papers, letters comments and replies.

HPV vaccine vs other vaccine or placebo or no vaccine

The most frequent ADs observed across the six studies were musculoskeletal (e.g. systemic lupus erythematosus), CNS conditions and endocrinological conditions (especially thyroid disease). The results of the meta-analysis demonstrated that ADs were not significantly more frequent in subjects receiving HPV vaccines than in those receiving placebos (pooled OR 1.038, 95% CI 0.689-1.562 (Fig. 2).

The Cochran Q test (67.68; $p < 0.001$; GdL = 5) showed heterogeneity for many characteristics:variability, sample size in individual jobs etc. The Higgins index (92.61%) also showed significant heterogeneity. For this reason, the choice fell into a "random" model with an odds ratio of 1.038 and 95% CI of 0.689-1.562.

Analysis of the forest plot reveals that almost all publications fall on the line of no effect, except for the study by David A. Geier (OR = 2.186; CI 95% 1.757-2.720), or 2.65% of vaccinated subjects with autoimmune dis-

ease versus 1.23% of unvaccinated subjects with autoimmune disease.
The funnel plot also showed a wide variability in the data (Fig. 3).
In the study by Geier et al. was observed that cases of autoimmune disease (such as gastroenteritis, arthritis, systemic lupus erythematosus, vasculitis, alopecia or CNS conditions) were significantly more likely than controls to have received the HPV4 vaccine. Casess with Guillain-Barre syndrome or thrombocytopenia were no more likely than controls to have received the HPV4 vaccine [15]. In the study by Verstraeten et al. the autoimmune events observed included thyroid disease (the most common), LES, and neuroinflammation (multiple sclerosis and optic neuritis). For each disease category or for any individual event, most relative risks were close to 1 and all the 95% CIs included. The overall relative risk was 0.92 (95% CI: 0.70, 1.22). The highest relative risk for an individual event was 2.39 for systemic lupus erythematosus and the lowest were 0.53 for diabetes mellitus and nephritis. The 95% CIs of the relative risks of these events all included 1, suggesting no significantly increased or decreased risk following administration of the HPV-16/18 vaccine [16].
In the study by Block et al. no significant difference in AD rates were noted between vaccine and placebo recipients The most common autoimmune conditions were arthralgia, hypothyroidism and psoriasis [18].
In the study by Grimaldi Bensouda et al. there was no evidence of an increased risk of the studied ADs following vaccination with Gardasil within the time periods studied. The ADs included idiopathic thrombocytopenic purpura, central demyelination/multiple sclerosis, Guillain-Barrè syndrome, connective tissue disorders, type 1 diabetes mellitus and autoimmune thyroiditis [17].
In the study by Willame et al. the odds ratio (OR) (95% CI) of ADs was 1.41 in female and 1.77 in male cohorts when compared to the respective female and male historical cohorts. Secondary endpoints were evaluated for the following diseases with > 10 cases: Crohn's disease (OR: 1.21 for female and 4.22 for male cohorts); autoimmune thyroiditis (OR: 3.75 for female and no confirmed cases for male cohorts) and type 1 diabetes (OR: 0.30 for female and 2.46 for male cohorts). Analysis using confirmed and non-confirmed cases showed similar results, except for autoimmune thyroiditis in females, OR: 1.45 (0.79 to 2.64) [20].
In the study by Angelo et al. the incidence of unsolicited AEFI reported within 30 days after administration was similar between HPV and Control groups (30.8% and 29.7%). The most frequently reported events within one year of administration were: psoriasis, Grave's disease, autoimmune thyroiditis and vasculitis, rheumatoid arthropathies and neuritis. The OR for each event showed no increased risk for women vaccinated with HPV vaccine [19].

Discussion

The objective of this meta-analysis was to assess the onset of autoimmune conditions related to HPV vaccines. References were included if they reported a RCT of HPV vaccines, including a placebo control group and gave information regarding the onset of ADs [15-20].
We identified three studies reporting on bivalent HPV vaccines and three studies on quadrivalent vaccines. The total number of subjects included in the meta-analysis comprised 243,289 in the vaccine group and 248,820 in control groups (another vaccine or no vaccine).
Four of the six trials had a Jadad score of 3 or 4 indicating an adequate trial quality [17-20].
ADs were reported by all studies. However, none of the observed events were considered to be related to the use of HPV vaccine.
The results of the meta-analysis should be interpreted with caution due to the several limitations.
First the number of the included clinical trials meeting the inclusion criteria was limited; second due to the different geographical locations of the RCTs included in our study and the Higgins index obtained, we chose a random-effects model for the meta-analysis which further widens the confidence intervals. Differences in the

Fig. 2. Forest plot.

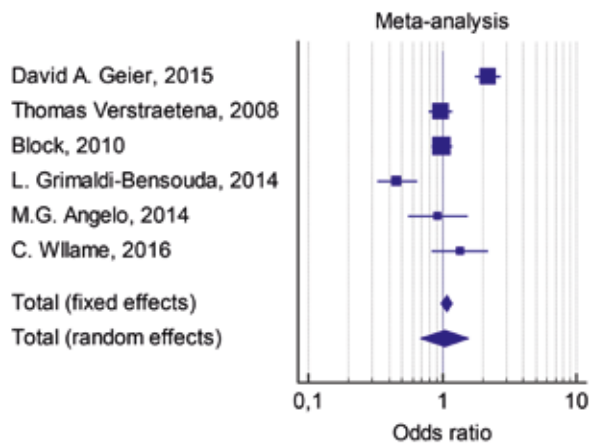
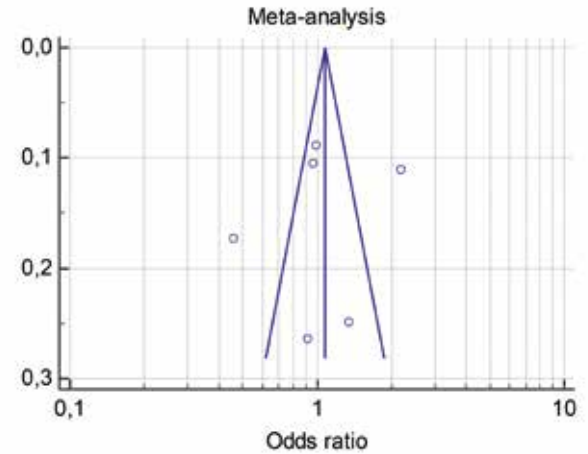


Fig. 3. Funnel plot.



reporting method of observed ADs and the different ADs reported also limit the results of the study.
Vaccine administration is usually safe and serious adverse events rare. In the past, the hypothesis of a correlation between the Hepatitis B vaccine and MS in adolescents, supported by reports of temporal association between vaccine shot and disease onset was sufficient to fuel controversies on the use of vaccine in subjects with other ADs [21-24]. This lesson about the effect of publications about possible links between ADs and a vaccine should thus be considered when the safety of a vaccine is debated; the risk of misinterpretation of association is particularly high when we consider autoimmune disease and the HPV vaccine, because this vaccine is recommended for young females (but also for males) in whom the incidence of autoimmune disease is high [25].
Therefore the role of pharmacovigilance surveillance remains of fundamental importance in allowing the scientific community to detect unknown or rare events possibly related to the vaccine.
A recent report highlighted the possible role of a genetic predisposition to vaccine-induced autoimmune disease [26]. The presence of genetic bases for adverse events has been described for several drugs; perhaps one of the most important being the HLA-B*57:01 for a nucleoside inhibitors of reverse transcriptase (abacavir) [27]. The identification of genetic bases for adverse events following vaccination should be actively investigated as this would provide a useful tool to prevent rare and serious diseases without impacting negatively on public confidence in immunisation programmes. Furthermore, many cases of ADs reported in the literature were sporadic cases appearing in articles such as "case reports". It is therefore necessary to clarify whether any relation exists between the administration of the vaccine and the onset of ADs (this would not seem to be so from our meta-analysis) or whether there is a mere coincidence in a subject destined to developed an ADs [28-30].
Today, concerns about vaccine safety have led some parents to decline recommended vaccination of their children, carrying to the spread of a phenomena called "vaccine hesitancy" and leading to the spread of diseases, as measles in Italy [31]. So study about the reassurance of vaccine safety remains critical for population health. In the literature, many reviews and meta-analysis analyzed the vaccine safety and one evidenced that there aren't association between some vaccines and AEFI as autism and leukemia, but show an association with some vaccines, such as intussusception after rotavirus vaccine or febrile seizure post MMR or MMRV vaccine [32-34].
These AEFI are extremely rare, many factors could be implicated and should be evaluated against the protective benefits provided by the vaccines.

Conclusions

No major ADs were identified for bivalent and quadrivalent HPV vaccines. Therefore, further studies are needed, particularly with accurately defined and reported safety outcomes to better evaluate the risks of these vaccines. In future, we also aim to investigate the implications of HPV vaccines for the most commonly reported individual ADs.

Acknowledgements

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Conflict of interest statement

None declared.

Authors' contributions

All authors carried out a systematic review to identify all scientific publications dealing with the correlation between vaccine anti-papillomavirus and new onset of autoimmune diseases. Screening was carried out independently by two authors (RS, CG). Any disagreement about eligibility between reviewers was resolved by a third author (VLF). The first two authors extracted data from included papers using a data extraction form reviewed by the other co-authors. Two independent reviewers (CG and RS) identified potentially relevant articles, collected the data and independently assessed the quality of individual studies included in the meta-analysis. GT and CG make data analysis.

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■ Correspondence: Raffaele Squeri, Department of Biomedical Sciences and Morphological and Functional Images, AOU Policlinico G. Martino, Torre Biologica, University of Messina, via Consolare Valeria, 98125 Messina, Italy - E-mail: raffaele.squeri@unime.it