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Pharmacovigilance analysis of spondyloarthritis following HPV vaccination based on the VAERS database

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HPV vaccine is an important biological product that contributes to disease prevention and control and public health system construction, and it shows an increasing vaccination rate year by year. Based on this high vaccination rate, it has brought about many adverse events. The aim of this study was to investigate the association between real world HPV vaccine and spondyloarthritis. Data from Vaccine Adverse Event Reporting System (VAERS) through January 1, 2025 were included in the study. Four pharmacovigilance analysis methods and bonferroni corrected P-values were utilized to uncover associations between HPV vaccines and spondyloarthritis. In addition, subgroup analyses were utilized to explore populations with different characteristics. Complementarily, time to induction analysis and Weibull distribution analysis were utilized to expand the research horizons. Of the 60,840 HPV vaccine-related adverse events recorded in the VAERS database during the study period, 141 could be attributed to spondyloarthritis. Of these, juvenile idiopathic arthritis and reactive arthritis were monitored for warning signs of positive significance. The results of the subgroup analysis showed that the gender was female and the age group was lower was found to have higher positive signals for adverse events. Weibull distribution analysis showed that the vaccine had an early-onset profile, HPV vaccine-induced spondyloarthritis was progressive and decreasing over time. This study suggests an association between HPV vaccine and spondyloarthritis with different predisposing risks in different patient populations and treatment stages. Patients should be closely monitored for spondyloarthritis-related markers and assessed for risk during HPV vaccination. This study provides more comprehensive insights into HPV vaccine safety and the understanding of spondyloarthritis.

Keywords HPV vaccine, VAERS, Spondyloarthritis, Juvenile idiopathic arthritis, Reactive arthritis

Abbreviations

HPV	Human papillomavirus
VAERS	Vaccine Adverse Event Reporting System Spondyloarthritis (SpA)
PT	Preferred terms
ROR	Reporting odds ratio
PRR	Proportional reporting ratio
IC	Information component
EBGM	Empirical bayesian geometric mean
SOC	Systemic organ classes

Background

As an extremely common sexually transmitted disease pathogen globally, human papillomavirus (HPV) poses a major challenge to public health with a wide range of HPV types, with more than 200 identified, including high-risk (type 16, type 18 and so on) and low-risk (type 6, type 11 and so on), depending on their carcinogenicity[1]. Specifically, approximately 80% of individuals in the female population have a history of HPV exposure at some

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point in their life course[2,3]. Persistent infection with high-risk HPV induces abnormal proliferation of cervical epithelial cells, which can lead to malignant transformation and ultimately to cervical cancer. As the fourth most common cancer in women, cervical cancer causes more than 300,000 deaths worldwide each year[4]. In addition, persistent infection with high-risk HPV is closely associated with malignant tumors such as anal and oropharyngeal cancers[5]. Complementarily, low-risk HPV is not carcinogenic but can cause genital warts, which also seriously affects the quality of life of patients[6]. Given the high prevalence of HPV infection and the severity of the diseases caused by it, the development and promotion of HPV vaccines are of key importance in the field of primary tumor prevention.

At this stage, there are three main types of prophylactic vaccines for HPV, namely the bivalent HPV vaccine, the quadrivalent HPV vaccine, and the nine-valent HPV vaccine[7]. In the United States, HPV vaccinations are primarily administered in primary care and medical facilities, and these vaccines are effective in preventing 90% of HPV infections and have been shown to have a coverage rate of more than 75%[7,8]. However, it is worth noting that based on this high vaccination rate, a number of adverse events have been identified. In addition to common systemic reactions such as fever, nausea, and headache, the potential risk of autoimmune disease due to HPV vaccine is gradually raising concern[9,10].

Spondyloarthritis (SpA), as a group of autoimmune diseases characterized by inflammation of the mid-axial joints, includes subtypes such as juvenile idiopathic arthritis and reactive arthritis. Its clinical symptoms are dominated by inflammatory low back pain, and with the progression of the disease, it can lead to spinal ankylosis and deformity, which seriously affects the patient's activity function[11]. In addition, there are significant regional differences in the prevalence of SpA, with a prevalence of 0.20% (95%CI: 0.00–0.66%) in Southeast Asia and a value as high as 1.61% (95%CI: 1.27–2.00%) in the Arctic[12]. Complementarily, the pathogenesis of this spectrum of diseases is highly correlated with the HLA-B27 gene and involves dysregulation of the immune response triggered by microorganisms[13]. Recent studies have shown that some vaccines can activate autoimmune pathways and thus induce related diseases through molecular mimicry mechanisms[14]. This provides a new direction for thinking about the association between HPV vaccines and their risk of adverse events, suggesting that HPV may have a potential risk of inducing spondyloarthritis.

Although the safety of HPV vaccine has been widely proven, however, sufficient clinical evidence for its association with SpA is still lacking. In this study, we conducted an in-depth investigation with the Vaccine Adverse Event Reporting System (VAERS), which is jointly managed by the U.S. Food and Drug Administration and the U.S. Centers for Disease Control and Prevention, and systematically analyzed the reported signals related to spondyloarthritis after HPV vaccination. Through in-depth mining and analysis of real world data, this study aims to identify potential associations between HPV vaccines and SpA, and thus provide new perspectives and data support for comprehensive and accurate assessment of HPV vaccine safety and effective prevention of autoimmune risks.

Methods

Data sources

This study included HPV vaccination data through January 1, 2025 from the open-source VAERS, a key component of the U.S. Vaccine Safety Surveillance Program whose data are available online[15]. Specifically, VAERS accepts reports from multiple sources, including health care providers, patients, parents of patients, and others. Reports cover a wide range of topics, including demographic information, dates of vaccinations and adverse events, brief medical histories, and diagnoses of post-vaccination adverse events.

Procedures

We reviewed reports of spondyloarthritis following HPV vaccination, which covered psoriatic arthritis, enteropathic arthritis, reactive arthritis, juvenile idiopathic arthritis and ankylosing spondylitis. Further subgroup analyses were implemented to provide insight into the impact of different characteristics on the findings. In the gender subgroup dimension, it was divided into males and females. In terms of age stratification, vaccinees younger than 60 years of age were defined as the younger age group, and those aged 60 years and above were categorized as the older age group. At the same time, this study categorized the proportion of cases with serious consequences of HPV vaccination and the time of induced adverse events to deepen the identification of the safety characteristics of this vaccine. Furthermore, due to the inherent characteristics of VAERS, a passive surveillance system, all data within the database may be associated with reporters' subjective biases or the recording practices of healthcare institutions, exhibiting a pattern of Missing Not at Random. Imputation methods, such as mean imputation and multiple imputation, rely on strong assumptions, like the missingness mechanism being independent of observed values, which may introduce biases. To avoid distorting results caused by unmet assumptions in imputation models, we ultimately opted to remove missing values from our dataset. It is important to note that for each included report, professionals at VAERS and its partner organizations used the Medical Dictionary of Regulatory Activities to assign one or more preferred terms (PT) to the report to standardize measurements and improve data precision[15]. Additionally, submitting false VAERS reports is a violation of U.S. federal law and is punishable by fines and imprisonment to ensure a high degree of consistency and reliability in the data collection process.

Statistical analysis

In defining and identifying adverse events, this study used the four methods of reporting odds ratio (ROR), proportional reporting ratio (PRR), information component (IC) and empirical bayesian geometric mean (EBGM) to conduct the analysis in a synergistic manner. In order to comprehensively screen for potential safety hazards, reports meeting the positive signal value of any of the methods were recognized as positive adverse event reports, and the specific calculation formula is detailed in Table S1[16]. In view of the multiple analytical

methods used in the study, to avoid the Class I error caused by multiple comparisons, the bonferroni method was used to correct the calculated P values to improve the accuracy and reliability of the results. After completing the standardized data preparation, the study will focus on baseline and subgroup data mining to gain in-depth insight into the value of specific population data. At the same time, Weibull distribution analysis will be used to dynamically analyze the trajectory of adverse event rates from the time dimension to broaden the research horizon (Fig. 1). Finally, in order to ensure that the analysis process is efficient, accurate and reproducible, R 4.4.2 and the integrated development environment Rstudio are used for data processing and analysis.

Results

Descriptive analysis

As of January 1, 2025, information on 60,840 patients with adverse events related to HPV vaccination was included in the VAERS database (Table 1). Of these, quadrivalent HPV vaccine-related adverse events were reported in the highest number (n = 37,266, 61.3%), followed by the nine-valent HPV vaccine (n = 16,592, 27.3%) and bivalent HPV vaccine (n = 4,710, 7.7%). When focusing on spondyloarthritis-related cases, 141 such data were reported in the database. Complementarily, 17.0% of all HPV vaccine adverse event reports during the study analysis period were categorized as serious reports, specifically 6,893 (11.3%) for hospitalization and 3,457 (5.7%) for disability.

Disproportionality analysis

When focusing on the statistical classification at the systemic organ classes (SOC) level, a total of 27 organ systems were affected by HPV vaccination. Of these, general disorders and administration site conditions had the highest percentage, while congenital, familial and genetic disorders were at the bottom of the quantitative scale (Fig. 2). In terms of signal intensity, pregnancies, puerperium and perinatal conditions presented the strongest level of positive signal (ROR = 4.26, 95%CI: 4.04–4.49). Complementarily, when focusing on spondyloarthritis, the systematic classification was concentrated in the SOC of musculoskeletal and connective tissue disorders. And when focusing on the PT level, two spondyloarthritis adverse events were monitored for meaningful positive signals. Among them, juvenile idiopathic arthritis was the adverse event with the highest number of occurrences and it corresponded to an adverse event with a higher alert signal value (ROR = 30.47, 95%CI: 22.45–41.35, P < 0.001) and a stronger signal intensity than reactive arthritis (ROR = 2.06, 95% CI: 1.47–2.88, P < 0.001) (Table S2, Fig. 3).

Based on the subgroup stratification analysis method, the present study further delved into the potential associations between the two types of spondyloarthritis adverse events, which presented positive signals at the PT level, and HPV vaccine. Notably, in the gender subgroup, only juvenile idiopathic arthritis adverse events (ROR = 6.21, 95%CI: 0.84–45.85, P = 1.000) were reported to be positive in the male group, whereas juvenile idiopathic arthritis (ROR = 28, 95%CI: 19.82–39.56, P < 0.001) and reactive arthritis in the female group (ROR = 2.46, 95%CI: 1.72–3.53, P = 0.005) were reported. In addition, for different age groups, spondyloarthritis-

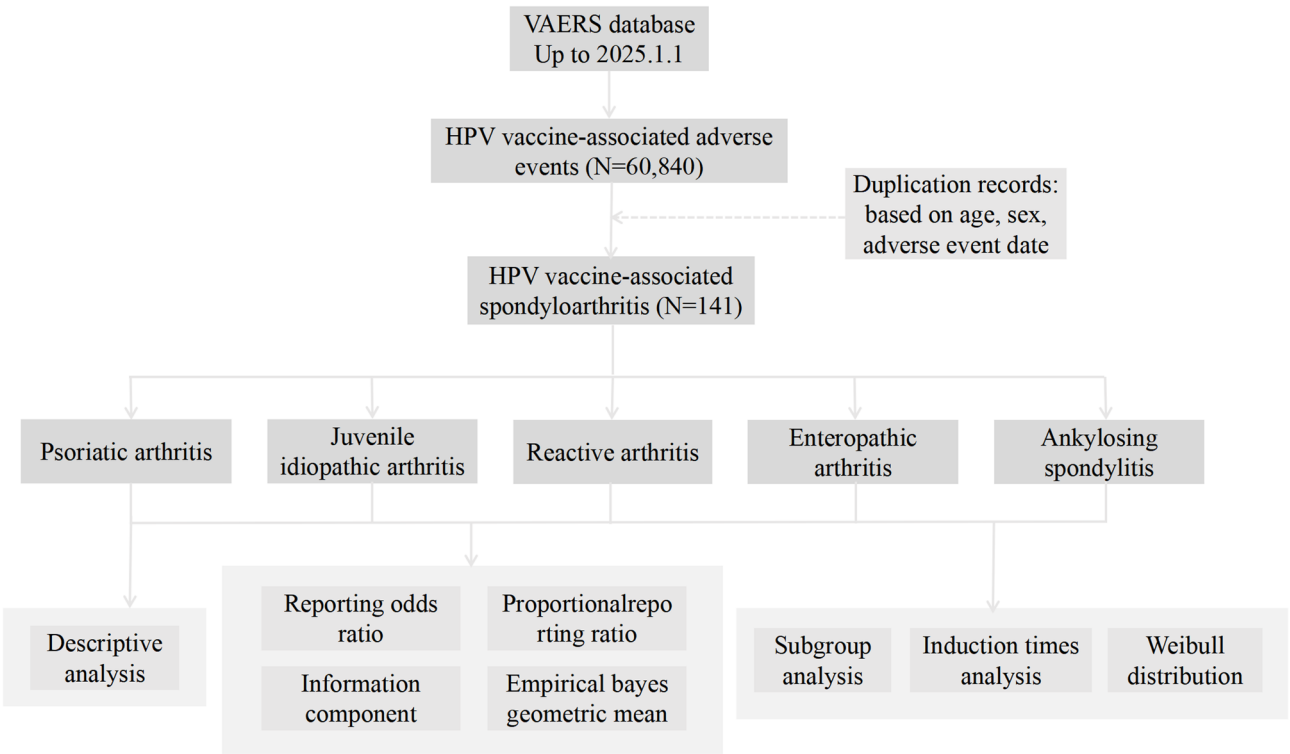

Fig. 1. Flow chart showing the analysis process of the study.

Characteristic	Frequency (*N*)	%
Patients	60,840	
Gender		
Female	42,239	69.4%
Male	5,703	9.4%
Unknown	12,898	21.2%
Age (year)		
< 18	24,615	40.5%
18–64.9	13,844	22.8%
65–85	59	0.1%
> 85	3	0.0%
Unknown	22,319	36.7%
Serious/non-serious status		
Serious	10,349	17.0%
Non-serious	50,491	83.0%
Jurisdictions		
Alaska	68	0.1%
Alabama	272	0.4%
Arkansas	192	0.3%
American Samoa	1	0.0%
Arizona	641	1.1%
California	3,344	5.5%
Colorado	532	0.9%
Connecticut	461	0.8%
District of Columbia	76	0.1%
Delaware	129	0.2%
Florida	1,669	2.7%
Federated States of Micronesia	2	0.0%
France	17,829	29.3%
Georgia	709	1.2
Guam	7	0.0%
Hawaii	109	0.2%
Iowa	257	0.4%
Idaho	153	0.3%
Illinois	1,223	2.0%
Indiana	522	0.9%
Kansas	246	0.4%
Kentucky	430	0.7%
Louisiana	337	0.6%
Massachusetts	832	1.4%
Maryland	747	1.2%
Maine	187	0.3%
Marshall Islands	1	0.0%
Michigan	1,170	1.9%
Minnesota	465	0.8%
Missouri	571	0.9%
Northern Mariana Islands	1	0.0%
Mississippi	101	0.2%
Montana	80	0.1%
North Carolina	751	1.2%
North Dakota	95	0.2%
Nebraska	154	0.3%
New Hampshire	193	0.3%
New Jersey	1,460	2.4%
New Mexico	262	0.4%
Nevada	239	0.4%
New York	2,058	3.4%
Continued		

Characteristic	Frequency (*N*)	%
Ohio	1,187	2.0%
Oklahoma	285	0.5%
Oregon	357	0.6%
Pennsylvania	2,267	3.7%
Puerto Rico	80	0.1%
Palau	1	0.0%
Rhode Island	202	0.3%
South Carolina	312	0.5%
South Dakota	98	0.2%
Tennessee	445	0.7%
Texas	2,051	3.4%
Utah	259	0.4%
Virginia	1,022	1.7%
Virgin Islands	9	0.0%
Vermont	60	0.1%
Washington	585	1.0%
Wisconsin	447	0.7%
West Virginia	192	0.3%
Wyoming	50	0.1%
Missing	12,355	20.3%

Table 1. The clinical distribution characteristics of adverse events reported for HPV vaccination. *N*, number of adverse event reported.

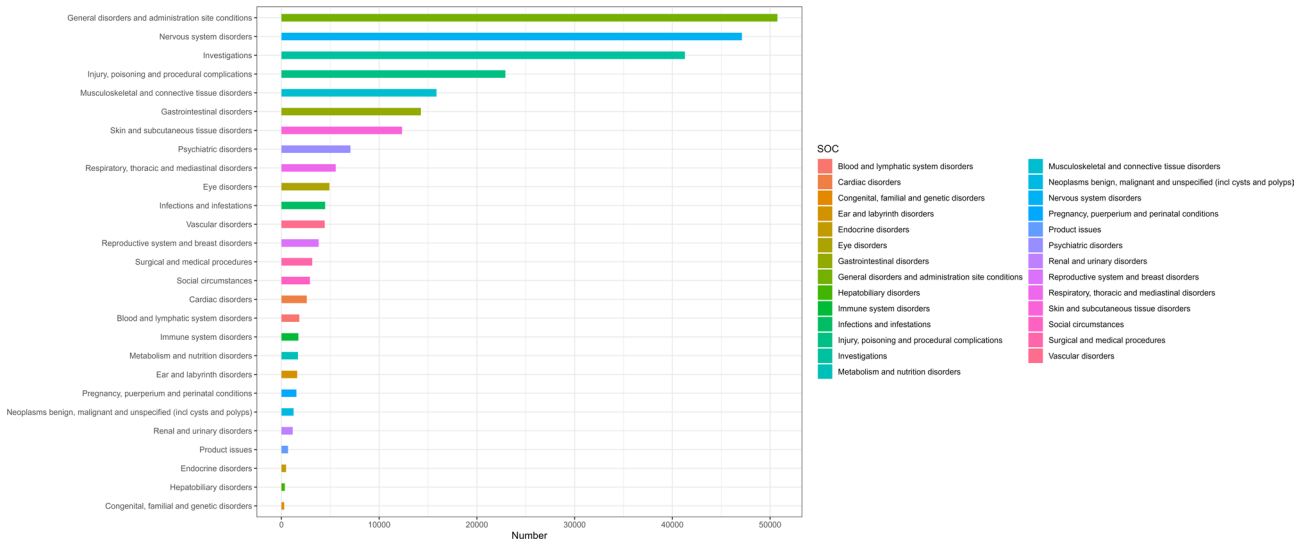

Fig. 2. Bar plot depicting the distribution of adverse events for HPV vaccine at the SOC level.

related adverse events were found only in the younger age groups, where juvenile idiopathic arthritis (ROR = 23.53, 95%CI: 15.76–35.11, $P < 0.001$) and reactive arthritis (ROR = 3.24, 95%CI: 2.21–4.73, $P < 0.001$) presented a positive signals.

Time-to-onset analysis and Weibull distribution analysis

Our study collected data on 66 cases of spondyloarthritis that reported the time of onset of the disease, with a mean induction time of 63.42 days, while the median induction time was 19.50 (Q1 = 6.25, Q3 = 65.00) days (Fig. 4). Specifically, such adverse events occurred more often within one month, with a higher percentage occurring on the day of vaccination (n = 10,15.15%), and only a small percentage of patients experienced an adverse event of spondyloarthritis after 1 month of vaccination (n = 27, 40.91%). Finally, the results of the Weibull distribution showed that the two positive spondyloarthritis adverse events caused by HPV vaccination decreased over time, exhibiting an early failure type curve (Table 2).

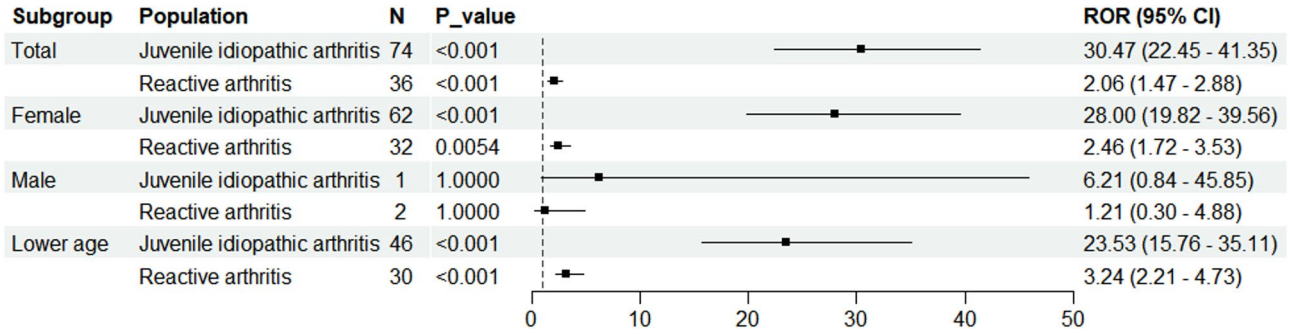

Fig. 3. Forest Plot showing spondyloarthritis-related adverse events reported by HPV vaccines in all subgroups.

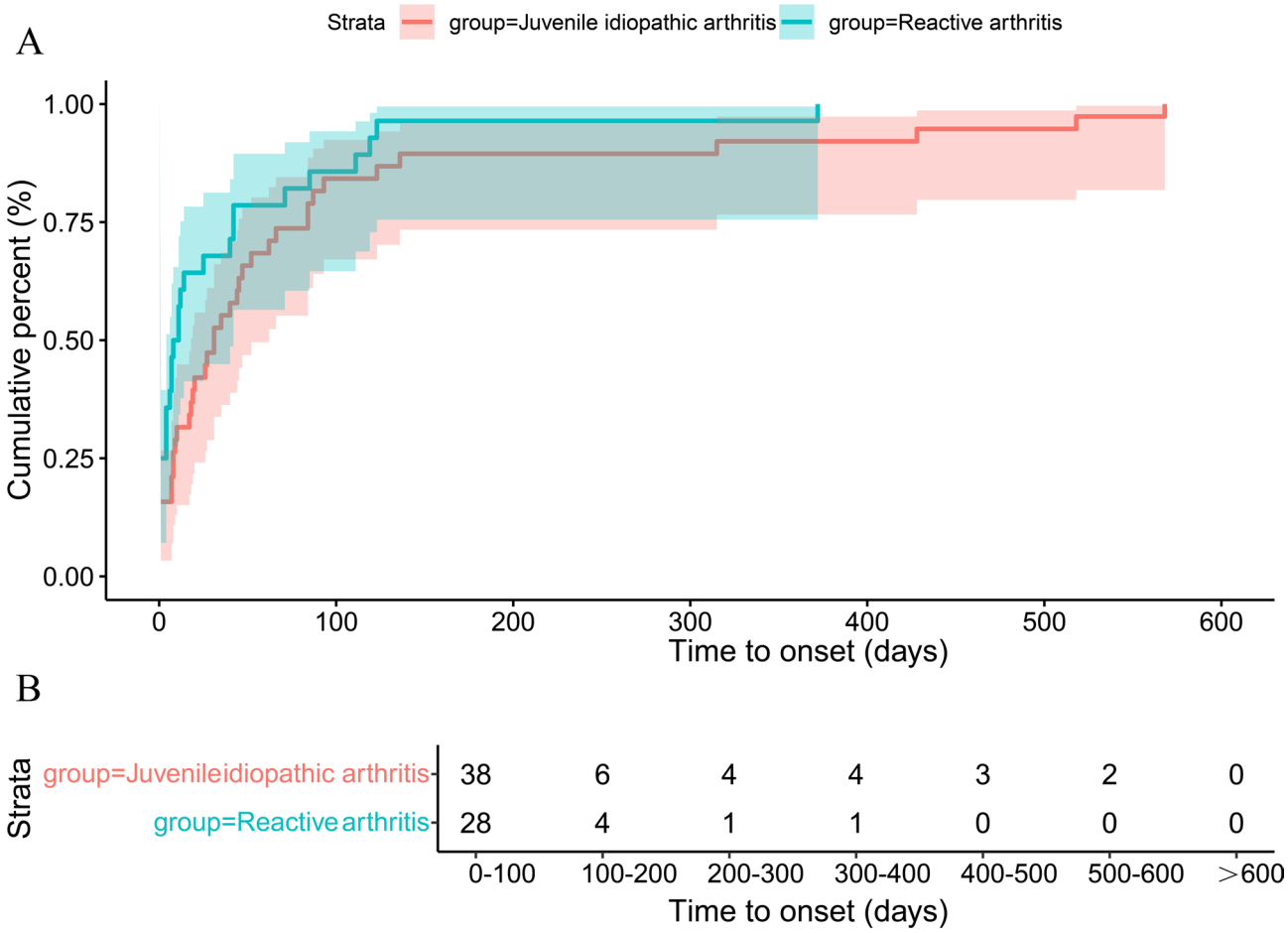

Fig. 4. (**A**) Cumulative incidence curve of HPV vaccination by time-to-onset. The different color lines indicate two spondyloarthritis adverse events, and the different color areas indicate the 95%CI of the value. (**B**) Distribution numbers of HPV vaccination by time-to-onset.

PTs	Shape parameter (95% CI)	Scale parameter (95% CI)	Type
Juvenile idiopathic arthritis	0.76 (0.57–0.95)	76.17 (39.73–112.61)	Early failure
Reactive arthritis	0.69 (0.48–0.90)	36.61 (13.58–59.63)	Early failure

Table 2. Weibull parameter test for positive spondyloarthritis associated with HPV vaccine. *CI*, confidence interval; *95% CI*, two-sided for Shape parameter and Scale parameter.

Discussion

HPV vaccines provide a critical line of defense for public health safety worldwide, and are important biologics that contribute to disease prevention and control and public health systems[7]. However, based on its increasing vaccination rate year by year, some of its potentially induced adverse events have been gradually discovered[17]. In this paper, we conducted a study and analyzed HPV vaccines with the aim of monitoring more comprehensively the potential risk of inducing adverse events in spondyloarthritis during the clinical use of such vaccines. Our results suggest an association between HPV vaccination and adverse events in spondyloarthritis in the population. Specifically, in the overall population, a warning signal of positive significance was shown between HPV vaccination and two types of spondyloarthritis adverse events, juvenile idiopathic arthritis and reactive arthritis.

Spondyloarthritis is a disease triggered by a combination of factors that synergize with each other during its onset and progression. Molecular mimicry mechanisms are considered to be one of the key factors contributing to the pathogenesis of spondyloarthritis[18]. Specifically, the heptapeptide sequence TLQANKS of the HPV L1 protein shares identical amino acid sequences with human basement membrane protein LAMA1[19]. This sequence homology may lead to immune system misidentification, causing the body to erroneously recognize its own joint tissues as foreign antigens and initiate an immune response. Notably, LAMA1 is a crucial component of articular cartilage; abnormal immune recognition of LAMA1 - derived peptides could potentially trigger cartilage inflammation, which is potentially associated with the joint erosion process characteristic of spondyloarthritis. Although direct evidence of binding between the HPV L1 protein and HLA - B27 molecules has not been found, a significant proportion of endogenous peptides presented by HLA - B27 originate from joint tissue proteins such as vimentin and cartilage glycoproteins[20]. This suggests that L1 - homologous peptides may undergo cross - presentation via the molecular mimicry mechanism, thereby activating joint - targeted cellular responses. Furthermore, evidence supports an indirect association between HPV L1 - shared peptides and extra - articular manifestations of spondyloarthritis. Since LAMA1 is expressed not only in joint tissues but also contributes to the formation of vascular basement membranes, an immune response against LAMA1 may explain cardiac involvement and skin lesions observed in some spondyloarthritis patients[19,21]. In addition, HPV vaccines may also induce abnormal activation of the immune system due to their adjuvant components, leading to spondyloarthritis with autoimmune characteristics[22,23]. Specifically, adjuvant components of HPV vaccines, such as aluminum salts and ASO4 complexes, can trigger abnormal immune responses through the pathogen-associated molecular patterns and damage-associated molecular patterns pathway[24]. Studies have shown that after HPV vaccination, vaccine adjuvants can activate mast cells, which leads to histamine release and immune dysregulation, thus activating the immune system[25]. Of interest, juvenile idiopathic arthritis and reactive arthritis are both highly associated with the HLA-B27 gene[26]. Given the high affinity of HLA-B27 and the low sensitivity of regulatory T cells to it, individuals carrying the HLA-B27 gene may have a relatively sensitized immune system, which provides further rationale for the development of spondyloarthritis[27]. The interaction of the multiple factors mentioned above ultimately disrupts the homeostatic state of the immune system and triggers adverse spondyloarthritic events.

The results of the gender subgroup showed that among the adverse events of spondyloarthritis due to HPV vaccine, the number of such adverse events and the intensity of warning signals were higher in the female group than in the male group. The reason for this result is related to the significantly higher vaccination coverage in females than in males, creating a larger surveillance base[28]. In addition, in the female population, estrogen is able to enhance the body's adaptive immune response through the modulation of immune cells, such as B cells, T cells, and dendritic cells, which in turn exacerbates the risk of adverse events with autoimmune properties[29,30]. Further age subgroup studies revealed that after HPV vaccination, younger age groups exhibited higher numbers and stronger positive signals for spondyloarthritis adverse events compared to older age groups. In terms of disease pathogenesis, the onset of spondyloarthritis has a significant age predisposition, with peak incidence concentrated before the age of 60 years[11]. In terms of immune response characteristics, the immune system is generally more active in the younger age group than in the older age group. This active immune response may prompt the immune system to produce more antibodies and cytokines after HPV vaccination, thereby increasing the risk of immune-related adverse events[31,32]. In addition, the immune system of the senior population has developed a certain degree of immune tolerance due to long-term exposure to various pathogens and vaccines. This immune tolerance plays a buffering role to a certain extent, and can effectively mitigate the adverse effects of HPV vaccination in the senior population[33].

Analysis of the data related to the time of induction showed that the model of spondyloarthritis induced by HPV vaccination exhibits early-onset characteristics, and the incidence of adverse events due to it tends to decrease over time. This suggests that, despite the risk of spondyloarthritis associated with the use of HPV vaccine in clinical practice, the long-term safety of the vaccine can be guaranteed to a certain extent in patients who must receive the vaccine based on medical indications and on the premise of early prophylaxis.

Notably, despite the 9-valent HPV vaccine's theoretically higher immunogenicity, its reporting proportion of spondyloarthritis (SpA) (27.3%) is lower than that of the 4-valent vaccine (61.3%). similar data discrepancies have been observed in prior studies, which ultimately yielded meaningful conclusions[34]. We conducted a detailed analysis of this phenomenon. Firstly, temporal factors and surveillance biases significantly influence the data presentation. The 4-valent vaccine, used in the United States from 2006 to 2016, has undergone a longer safety surveillance period compared to the 9-valent vaccine, which was launched in 2014[7]. Delayed adverse events from the early recipients of the 4-valent vaccine continue to be added to the VAERS database. In contrast, data collection for the 9-valent vaccine has been concentrated over the past decade. This disparity in surveillance duration has led to a structural bias in the cumulative number of reports. Additionally, as an early HPV vaccine, the 4-valent vaccine likely attracted more safety attention from the public and professionals at its launch than the 9-valent vaccine, resulting in a higher rate of voluntary reporting. Secondly, differences in vaccine adjuvant

formulations and immunological characteristics contribute to this discrepancy. The adjuvant components in the early formulation of the 4-valent vaccine may have induced a higher proportion of adverse reactions[23]. Conversely, the 9-valent vaccine's optimized manufacturing process refined its adjuvant system, reducing the incidence of such local reactions.

This study has several significant advantages. First, relying on the VAERS database, its extensive and timely characteristics enable it to rapidly detect rare and serious safety problems, effectively overcoming the inherent limitations of clinical trials and providing rich and real-time data support for the study. Second, given the complex effects of combined vaccination on the suppression or enhancement of immune responses, this study focuses on HPV vaccination reports and excludes interference from combined vaccination data, thus guaranteeing the accuracy of the study results. Third, this study is the first to identify and deeply investigate the adverse event of spondyloarthritis associated with HPV vaccination. It provides a scientific basis for balancing the safety and potential risks of HPV vaccination across different patient populations. Additionally, the research offers valuable insights and perspectives for optimizing HPV vaccination strategies and enhancing the differential diagnosis of post-vaccination conditions. However, there are limitations in this study that cannot be ignored. On the one hand, the VAERS database is a passive surveillance system, and its data only come from patients and clinicians who voluntarily report information, which makes the study susceptible to the inherent bias of the passive surveillance system, such as omission and over-reporting. On the other hand, the present study could not exclude the potential interference of pre-existing SpA and other conditions on the results, nor did it control for confounding factors such as administration of other vaccines, comorbidities, and concurrent medications. In addition, because the data were obtained from a U.S. database, the study was limited to vaccines approved in the U.S., and there is a lack of data on vaccines approved in other parts of the world. Therefore, more rigorous prospective studies are needed to obtain more comprehensive and accurate conclusions.

Conclusion

The widespread use of HPV vaccines in clinical practice has raised concerns about their safety, and whether they cause adverse events in spondyloarthritis remains unclear at this stage. By analyzing the information in the VAERS database using different strategies, our results suggest that there is an association between HPV vaccines and adverse events in spondyloarthritis, with female gender and relatively young age as risk factors that may predispose to such adverse events. The incidence of such adverse events tended to decrease over time. This study helps to improve medical professionals' understanding of the safety of HPV vaccines and further provides valuable insights into the prevention and clinical practice of spondyloarthritis

Data availability

The datasets generated and analysed during the current study are available in the Vaccine Adverse Event Reporting System (VAERS) database, [https://vaers.hhs.gov].

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NY: Conceptualization, Methodology, Data curation, Visualization, Validation, Writing-Original Draft and Writing-Review & Editing. JKD: Formal analysis, Investigation, Data curation, Writing-Original Draft and Writing-Review & Editing. HYF: Writing-Original Draft, Writing-Review & Editing, Supervision and Funding acquisition.

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