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Research article

OAE-based data mining and modeling analysis of adverse events associated with three licensed HPV vaccines

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ABSTRACT

Purpose: Three licensed human papillomavirus (HPV) vaccines (Cervarix, Gardasil, and Gardasil 9) have been effectively used to prevent infection with oncogenic HPV types; however, many adverse events (AEs) have also been reported following their vaccinations. We assessed AE profiles after receiving the HPV vaccines based on the reported data from Vaccine Adverse Event Reporting System (VAERS).

Methods: The AE data associated with Cervarix, Gardasil, and Gardasil 9 were retrieved from VAERS database respectively. The combinatorial biomedical statistical methods were used to identify the statistically significant AEs. The Gamma-Poisson Shrinker (GPS) model with gender/age stratification was applied to ascertain the serious adverse events (SAEs) related to the three licensed HPV vaccines. The AE profiles were classified and represented by the Ontology of Adverse Events (OAE) for further analysis.

Results: As of July 31, 2020, VAERS recorded 3,112, 31,606, and 6,872 AE case reports for Cervarix, Gardasil, and Gardasil 9, respectively. Our Frequentist statistical methods identified 135 Cervarix-enriched AEs, 55 Gardasil-enriched AEs, and 17 Gardasil 9-enriched AEs. Based on the OAE hierarchical classification, these AEs were clustered in the AEs related to behavioral and neurological conditions, immune system, nervous system, and reproductive system. Combined with GPS modeling, 46 unique statistically significant SAEs were founded to be associated with at least one of the three vaccines.

Conclusions: Our study led to the better understanding of the AEs associated with the licensed HPV vaccines. The hypotheses on the cause and effect relationships between the HPV vaccination and specific AEs deserve further epidemiological investigations as well as clinical trial studies.

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted virus, and more than 200 HPV types have been identified so far [1, 2]. Many studies have shown that over half of sexually active women have been infected by one or more genital HPV types at some point in time [3]. Furthermore, HPV infection also appears to be very common in men, though it has not been studied as extensively as infection in women [4]. The persistent infection of high-risk HPV can lead to cancers of the cervix, penis, vulva, vagina, anus, and oropharynx [5]. Implementation of an HPV vaccination campaign along with cytological screening program has the best chance of decreasing the morbidity and mortality associated with the HPV-related dysplasia and cancers, especially for cervical cancer [6]. Currently, three licensed vaccines (i.e., Cervarix, Gardasil, and Gardasil 9) are used to prevent different HPV types [7]. Approved in 2006, Gardasil is a tetravalent vaccine against HPV6/11/16/18; Approved in 2009, Cervarix is a bivalent vaccine against HPV16/18; Approved in 2014, Gardasil 9 is a 9-avalent vaccine against HPV6/11/16/18/31/33/45/52/58. According to the recommendations from the U.S. Food and Drug Administration (FDA), Gardasil and Gardasil 9 can be administered to females as well as males, while Cervarix only be used for females; they are usually administered in people aged 9 through 26 years, and Gardasil 9 is also licensed for use in catch-up vaccination of unvaccinated adults (aged from 27 to 45 years).

To date, hundreds of million doses of prophylactic HPV vaccines have been administered worldwide, resulting in dramatically decreased HPV infection and associated diseases [8]. However, current vaccination coverage is still insufficient to achieve herd immunity [9]. One reason is

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the high cost, making these vaccines unable to meet the needs of low-income populations [10]; the other reason is that people often express rational or irrational concerns for vaccine safety, which leads to the low confidence in vaccination [11]. Actually, there is no serious safety accidents following immunization were medically confirmed to be related to the HPV vaccines [12, 13, 14, 15]. However, a series of adverse events (AEs) have emerged, and some of them may be serious and even fatal. For example, the most common AEs are injection-site AEs (e.g., swelling and erythema) and vaccine-associated systemic AEs (e.g., pyrexia and headache) [16, 17]; the serious adverse events (SAEs) such as premature menopause [18], postural orthostatic tachycardia syndrome [17], and juvenile idiopathic arthritis [19] have also been reported.

In this study, we investigated comparative profiles of AEs associated with the three licensed HPV vaccines according to retrieved data from the Vaccine Adverse Event Reporting System (VAERS) [20]. Based on combinatorial biomedical statistical methods, we aimed to mine statistically significant HPV vaccine-associated AEs, and then classified and analyzed these AEs using the Ontology of Adverse Events (OAE) [21]. Furthermore, we adopted Gamma-Poisson Shrinker (GPS) with gender/age stratification methods to ascertain potential relationships between HPV vaccination and special SAEs [22]. Overall, this is the first ontology-based study to systematically analyze AE profiles associated with the three licensed HPV vaccines.

2. Methods

The general project workflow was shown in Figure 1, which outlines different steps in this study. The details of these research processes are provided below.

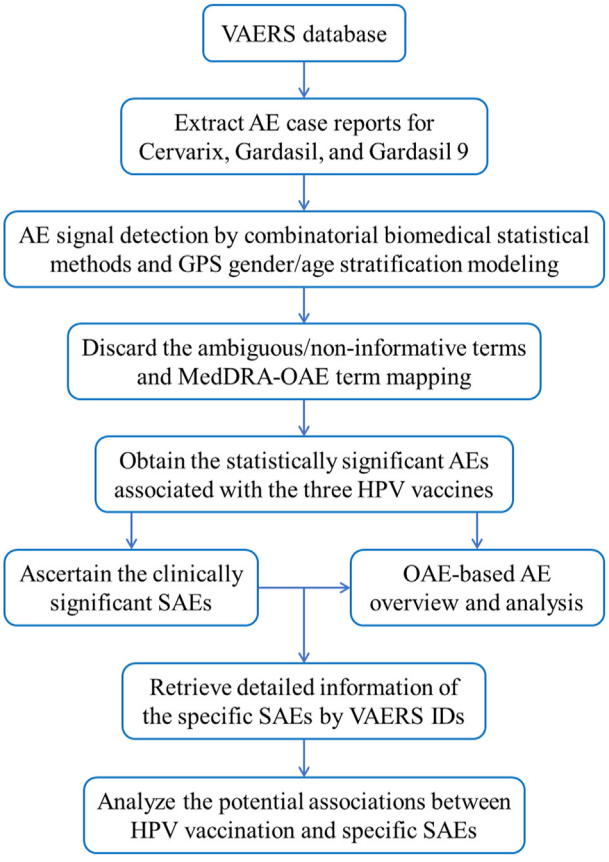

Figure 1. Overall project workflow. VAERS: Vaccine Adverse Event Reporting System; AE: adverse event; SAE: serious adverse event; HPV: human papillomavirus; GPS: Gamma-Poisson Shrinker; MedDRA: Medical Dictionary for Regulatory Activities; OAE: Ontology of Adverse Events.

2.1. Extraction of AE data from the VAERS database

VAERS is a spontaneous AE reporting system for licensed vaccines that is co-administered by FDA and the Centers for Disease Control and Prevention (CDC) since 1990 [20]. In VAERS, the AE was defined as a health problem that happens after vaccination, and the SAE is an AE that: (i) results in death, (ii) is life-threatening, (iii) results in hospitalization, (iv) results in disability or permanent damage, (v) is congenital anomaly or birth defect, (vi) requires intervention to prevent permanent impairment or damage, or other serious medical events [23]. By definition, the AE may or may not be caused by a vaccine. Therefore, VAERS data can be used to detect safety signals that might be related to vaccination, and cannot be used to determine if a vaccine caused an AE [20]. Anyone can submit an AE case report to VAERS, including health care professionals, vaccine manufactures, vaccine recipients, and parents or caregivers. The signs and symptoms in the AE case reports are coded using terms from the Medical Dictionary for Regulatory Activities (MedDRA), a standardized medical terminology for medical products (e.g., drugs and vaccines) [24].

The AE data in VAERS can be queried by different conditions such as symptom, vaccine characteristics, age and gender, vaccination date and report received date [25]. For the three HPV vaccines, we extracted the associated AE data accurately according to the vaccination information as shown in their FDA vaccine package inserts. Taking Cervarix as an example, the major search criteria include: the vaccine recipient's gender is female, the vaccinated age is 9–26 years old, and the report received date is from July 2009 to July 2020. Furthermore, we retrieved each individual case report for SAE (e.g., autoimmune disorder) according to the corresponding VAERS code to conduct descriptive analysis and review.

2.2. Combinatorial biomedical statistical methods

As a passive and numerator-only surveillance reporting system, VAERS is subject to a number of well-described limitations such as the lack of information on the total number of vaccines and the total number of people experiencing an AE [20]. The CDC and FDA generally use several statistical techniques like Empirical Bayesian data mining to analyze VAERS data to detect vaccine safety signals [26, 27]. In this study, we adopted the combinatorial biomedical statistical methods including Proportional Reporting Ratio (PRR), chi-square test ($x;^2$), and Base Level Filtration (BLF) to identify statistically significant AEs associated with the three HPV vaccines [28].

PRR calculates the proportion of a specific AE related to an HPV vaccine where the comparator is all other vaccines in VAERS. Chi-square test is used to determine whether a particular AE was significant among all the AEs associated with an HPV vaccine. BLF can filter out the background noises of primary data. The mathematical criteria used for a statistically significant AE is a PRR $\geq$2, $x^2 \geq 4$ and BLF $\geq$3 or 0.2% of total case reports (when the total case reports more than 1500) [27,29].

2.3. OAE-based AE profile analysis

In the VAERS database, all signs and symptoms of submitted AE case reports were coded using MedDRA terms. However, due to the fact that MedDRA lacks explicit term definitions and logical classification hierarchies, it is difficult to directly use the MedDRA-based AE information for automatic search and retrieval for further computational analysis and aggregation [30]. The OAE is a community-driven ontology developed to standardize and integrate data relating to AEs arising subsequent to medical interventions as well as to support computer-assisted reasoning [21]. OAE provides logically well-formed term definitions and an associated structured classification. The AE terms in OAE can be provided anatomic localization based on the location of symptoms as well as pathologically classified according to their clinical manifestations. For example, the AE of autoimmune encephalopathy is fit under *immune*

system AE or *brain AE*. OAE asserts only one parent term, and allows the other parent term(s) to be obtained automatically by reasoning. Thus, the *autoimmune encephalopathy AE* was asserted as a subclass of immune AE, and through reasoning (based on internal logical axiom definitions), it is inferred as a child term of *brain AE*. The reason of this choice is that the clinical outcome is often more critical to the physicians and the location can be easily defined using the UBERON anatomy ontology [31].

Previous studies have shown that OAE performed well than MedDRA in the analysis of AE data related to the licensed vaccines because it can avoid and resolve the issues existing in MedDRA mentioned above [28, 29, 32]. In this study, the MedDRA-coded statistically significant AEs were mapped to OAE by the given built-in term IDs, and then these AEs were classified and analyzed using the OAE ontological framework [21, 28]. We used the OntoFox software to automatically extract the hierarchical structures for the Cervarix, Gardasil, and Gardasil 9-specific AE terms [33]. Meanwhile, the detailed information for single AE (e.g., term definition and anatomic location) was retrieved through Ontobee software [34]. At last, the hierarchical results were all visualized and compared using the Protégé-OWL editor [35].

2.4. Gamma-Poisson Shrinker modeling for the statistically significant SAEs

The Gamma-Poisson Shrinker (GPS) data mining model has been used successfully for detection of special AEs in some spontaneous reporting systems [36]. In this study, we used an R package named 'openEBGM' [37], which is an implementation of the GPS model based on the Empirical Bayes approach for identifying the statistically significant SAEs related to the HPV vaccines in VAERS contingency tables. Since some rare SAEs tend to occur more frequently in the special age distribution and different genders, the algorithm of openEBGM with GPS targets to mine the SAEs associated with the HPV vaccines from gender and age stratifications [38]. In the openEBGM modeling process, the relative reporting ratio (*RR*) was selected to analyze the SAE counts in the contingency table. Model description as following:

The N_{ij} is actual count that represents the reported number of HPV vaccine-SAE pairs actually observed. The E_{ij} is expected count of the N_{ij}, which can be calculated in the contingency table by Eq. (1) [39]. We modeled the *RR* (λ_{ij}) to measure the observed-to-expected ratio (i.e., N_{ij}/E_{ij}). Since the *RR* is variable or imprecise when the number of reporting cases is small, the maximum likelihood estimation and Bayesian inference were used to adjust the *RR* based on the N_{ij} [39]. Each N_{ij} was modeled as random variable of Poisson distribution with unknown mean (μ_{ij}), i.e., $N_{ij} \sim$ Poisson (μ_{ij}). For estimate λ_{ij} (Eq. (2)), we assumed that λ_{ij} comes from a mixture of two parameterized gamma distributions, which include five parameters that can fit almost any empirical distribution [40]. Finally, the posterior distribution of the λ_{ij} is obtained through Bayesian inference and estimation, and then the *EBGM* values are actually derived from the expectation value of the logarithm of *RR* under the posterior probability distributions for each true *RR* (Eq. (3)).

$$E_{ij} = \frac{(a+b)(a+c)}{(a+b+c+d)} \tag{1}$$

$$\lambda_{ij} = \mu_{ij} \Big/ E_{ij} \tag{2}$$

$$EBGM_{ij} = e^{E[\log \lambda_{ij}]} \tag{3}$$

The *EBGM* score is the geometric mean of a posterior distribution of the true *RR*, and the EB_{05} is the fifth percentile of the Empirical Bayes Gamma Mixture. The $EB_{05} \geq 2$ was frequently cited as the signal metric threshold in the current analysis [41, 42, 43]. For the HPV vaccine-SAE pair, the $EB_{05} \geq 2$ may be interpreted to mean a potential causality, and the SAE has high enough specificity to deserve further investigation. Furthermore, compared with the Frequentist statistical methods mentioned above, the EB_{05} ensured the minimization of false positive signals. The Frequentist and Bayesian methods have no priority in AE data analysis, so that the two methods should be combined in practical application [44].

3. Results

3.1. Extracting AE profiles from VAERS cervarix, gardasil, and gardasil 9 data

As of July 31, 2020, in the VAERS database, there were 3,112, 31,606, and 6,872 AE case reports specifically related to the vaccination of Cervarix, Gardasil, and Gardasil 9, respectively. We extracted all of these case reports and stored them in Excel spread sheets. For mining the statistically significant AEs, we adopted the screening criteria including the *PRR* score ($\geq$2), x^2 score ($\geq$4), and the number of *BLF* (i.e., $\geq$6 for Cervarix, $\geq$ 63 for Gardasil, and $\geq$14 for Gardasil 9. Note that these cutoffs were 0.2% of total case reports, where were used since the total case reports for each vaccine were more than 1500). Furthermore, we found that some AE terms coded by MedDRA, such as 'white blood cell count normal', 'rheumatoid factor negative', and 'ultrasound scan' are ambiguous, non-informative, and/or indeed not AEs. As a result, these terms were discarded for the following analysis. At last, 135 Cervarix-specific statistically significant AEs, 55 Gardasil-specific statistically significant AEs, and 17 Gardasil 9-specific statistically significant AEs remained (Table 1). Significantly, the AEs of syncope and tonic clonic movements are two symptoms shared in all the three HPV vaccines (Table 1). In total, 169 unique statistically significant AEs were identified to be associated with at least one of the three HPV vaccines (Table 1).

Among all the statistically significant HPV vaccine AEs (Table 1), our analysis identified 26 SAEs associated with Cervarix (e.g., anaphylactic shock, autoimmune encephalopathy, and juvenile idiopathic arthritis), 15 SAEs associated with Gardasil (e.g., vasovagal syncope, spontaneous abortion, and ovarian cyst), and 4 SAEs associated with Gardasil 9 (e.g., unconsciousness, seizure, and urinary incontinence). Overall, we identified 36 statistically significant unique SAEs associated with the three HPV vaccines by the Frequentist methods, and they deserved an in-depth analysis in the following sections.

3.2. AEs hierarchical classification based on the OAE method

We analyzed the statistically significant AEs using the OAE-based classification method. Table 1 summarizes the clustering results based on the hierarchies of OAE. As shown in Table 1, the most frequently identified AE category for the three HPV vaccines is the *behavioral and neurological AE*, which includes 57 unique AEs. Specifically, the AEs clustered in the categories of *musculoskeletal or connective tissue AE* (e.g., cataplexy and myoclonus) and *immune system AE* (e.g., autoimmune encephalopathy and juvenile idiopathic arthritis) are relatively frequent to Cervarix (Table 1). Gardasil was associated with many AEs (e.g., amenorrhoea, ovarian cyst, and vaginal hemorrhage) that belong to *reproductive system AE* category (Table 1). It is remarkable that Cervarix has the most complicated AE hierarchical classification with the largest number of statistically significant AEs, while Gardasil 9 was associated with the least number of AEs and thus had a concise hierarchical classification.

Since Gardasil and Gardasil 9 could be vaccinated to females as well as males, we assumed that the AE profiles associated with the two vaccines had similarities and differences related to gender. As shown in Figure S1, Gardasil and Gardasil 9 both shared many AEs for both females and males, with the most commonly shared AEs enriched in the category of behavioral and neurological AE (e.g., movement disorder AEs and sensory capability AEs). For Gardasil (Figure S1a), there are many female-specific AEs enriched in the categories of digestive system AE (e.g., constipation and dyspepsia) and female reproductive system AE

Table 1. The statistically significant AEs associated with the three HPV vaccines.

Adverse Event	Vaccine	Count	*PRR*	x^2
Behavioral and neurological AE				
amnesia*	Gardasil	184	3.19	127.18
Aggression	Cervarix	10	3.84	17.27
cold sweat	Cervarix	66	2.54	54.35
disturbance in attention	Gardasil	456	4.21	438.91
	Cervarix	67	2.39	47.98
Dysaesthesia	Cervarix	7	2.58	5.89
Dyscalculia	Cervarix	16	31.40	169.60
Dysgeusia	Cervarix	13	2.77	12.70
Dysgraphia	Cervarix	11	5.89	33.50
Dysstasia	Cervarix	39	3.61	61.25
Fall	Gardasil 9	343	2.28	178.77
	Cervarix	291	3.93	535.17
Fear	Gardasil 9	14	2.31	7.32
	Cervarix	12	3.65	19.19
muscle contractions involuntary	Gardasil 9	22	2.31	11.44
hyperacusis	Gardasil	132	3.64	107.96
	Cervarix	38	4.09	72.34
injection site movement impairment	Cervarix	11	17.66	86.49
irritability	Cervarix	15	2.26	9.41
memory impairment	Gardasil	272	2.72	148.44
	Cervarix	110	5.96	342.03
mood swings	Gardasil	77	5.95	99.12
motor dysfunction	Cervarix	12	4.16	23.30
movement disorder	Cervarix	46	8.83	213.46
abasia	Gardasil	184	2.32	74.90
	Cervarix	28	2.27	17.68
abnormal gait	Cervarix	168	4.87	410.73
dyskinesia	Gardasil	512	2.03	154.85
	Cervarix	93	2.74	89.88
paralysis	Gardasil	120	2.21	43.70
	Cervarix	27	3.24	35.52
monoplegia	Cervarix	22	5.55	62.55
gaze palsy	Gardasil	305	2.70	164.51
	Cervarix	31	2.20	18.11
panic attack	Gardasil	87	2.24	32.71
	Cervarix	13	2.07	6.44
prosopagnosia	Cervarix	6	105.97	89.14
psychiatric disorder	Cervarix	12	3.79	20.27
agitation	Cervarix	7	2.42	5.16
cognitive disorder	Gardasil	176	3.60	142.31
	Cervarix	46	3.98	84.21
depression	Gardasil	286	4.01	260.98
emotional disorder	Cervarix	13	5.47	36.27
hallucination	Cervarix	16	3.36	22.37
schizophrenia*	Cervarix	7	17.66	55.03
seizure*	Gardasil 9	75	2.34	40.30
	Cervarix	92	2.59	79.40
epileptic seizure*	Gardasil	168	3.05	108.95
	Cervarix	48	4.79	113.66
abdominal distension	Gardasil	103	5.46	124.42
abdominal pain	Gardasil	1040	2.45	478.26
migraine	Gardasil	445	2.46	203.50
malaise	Cervarix	381	3.42	569.91
allodynia	Cervarix	6	3.93	10.71
fibromyalgia	Gardasil	87	2.77	48.58
	Cervarix	29	4.27	58.60
neuralgia	Gardasil	108	2.89	64.65
pelvic pain	Cervarix	7	2.33	4.71
parosmia	Cervarix	16	15.70	116.65
presyncope	Cervarix	380	9.69	1947.35
sensory disturbance	Gardasil	203	2.39	87.13
	Cervarix	59	3.99	108.54
syncope*	Gardasil 9	965	2.02	393.10
	Gardasil	4106	2.21	1622.78
	Cervarix	552	2.25	370.02
vasovagal syncope*	Gardasil	106	4.94	117.98
unconsciousness*	Gardasil 9	637	2.00	247.05
	Cervarix	487	3.31	697.22
unresponsive to stimuli	Gardasil 9	137	2.66	96.03
sleep disorder	Gardasil	250	2.19	90.12
	Cervarix	97	5.29	261.44
hypersomnia	Gardasil	169	2.19	60.31
	Cervarix	38	2.94	41.99
somatoform disorder	Cervarix	7	10.30	37.15
somnolence	Cervarix	87	2.80	87.79
tonic clonic movements	Gardasil 9	31	2.86	24.68
	Gardasil	161	3.37	119.91
	Cervarix	22	2.78	21.65
asterixis	Cervarix	6	105.97	89.14
Brain AE				
aphasia	Cervarix	14	2.78	13.79
Cardiovascular AE				
hypotension	Cervarix	78	3.48	116.05
cerebral hypoperfusion	Cervarix	10	29.44	103.04
orthostatic hypotension	Cervarix	16	5.77	47.58
arrhythmia	Cervarix	19	8.83	88.05
palpitations	Gardasil	454	2.38	195.29
bradycardia	Gardasil 9	17	2.11	7.12
	Cervarix	43	11.34	247.28
circulatory collapse*	Cervarix	21	5.08	53.54
circulatory shock*	Cervarix	50	20.07	424.78
anaphylactic shock*	Cervarix	20	7.85	82.85
neurogenic shock*	Cervarix	8	20.19	68.09
Digestive system AE				
retching	Gardasil 9	20	2.06	7.89
constipation	Gardasil	155	2.91	93.80
	Cervarix	31	2.67	28.26
dyspepsia	Gardasil	82	3.08	53.88
gastrointestinal disorder	Gardasil	83	2.34	34.11
gastritis	Cervarix	7	4.26	14.09
gastroenteritis*	Cervarix	11	6.27	35.97
gastrointestinal motility disorder	Cervarix	7	8.24	30.38
hematochezia	Cervarix	7	2.38	4.93
pharyngitis	Cervarix	10	2.26	6.27
oropharyngeal discomfort	Cervarix	6	9.63	30.05
stomatitis	Cervarix	10	4.42	21.15
Ear AE				
deafness	Cervarix	16	3.77	26.86
hypoacusis	Cervarix	14	2.21	8.24
tinnitus	Cervarix	41	2.72	38.92
Eye AE				
binocular eye movement disorder	Gardasil 9	123	2.26	61.43
swelling of eyelid	Gardasil 9	14	3.32	14.09
blindness transient	Cervarix	8	2.44	5.96

(*continued on next page*)

Table 1 (*continued*)

Adverse Event	Vaccine	Count	*PRR*	x^2
eyelid ptosis	Cervarix	7	3.09	8.43
nystagmus	Cervarix	9	5.89	27.40
photophobia	Cervarix	91	3.66	147.14
visual field defect	Cervarix	10	3.60	15.65
visual disturbance	Gardasil	65	2.70	34.92
Gustatory system AE				
hypophagia	Cervarix	7	4.26	14.09
Hair, skin or nail AE				
alopecia*	Gardasil	348	5.63	431.91
cyanosis	Cervarix	49	4.06	92.41
photosensitivity reaction	Cervarix	30	9.14	143.47
butterfly rash	Cervarix	8	10.09	41.72
erythema multiforme	Cervarix	6	2.36	4.13
pallor	Gardasil 9	565	2.30	304.74
	Cervarix	381	3.19	505.47
skin disorder	Gardasil	64	3.20	44.44
acne	Gardasil	104	4.53	107.16
Hematopoietic system AE				
anemia	Gardasil	111	2.34	45.92
	Cervarix	19	2.40	13.66
thrombocytopenia*	Gardasil	75	2.09	24.08
	Cervarix	13	2.94	14.323
Homeostasis AE				
hyperpyrexia	Cervarix	7	3.09	8.43
hypothermia	Cervarix	8	12.85	50.61
angioedema	Cervarix	16	2.36	11.03
face edema	Cervarix	11	3.53	16.66
laryngeal edema	Cervarix	6	10.60	32.60
Immune system AE				
autoimmune encephalopathy*	Cervarix	9	158.96	141.29
systemic lupus erythematosus*	Gardasil	90	3.63	73.33
	Cervarix	24	4.33	49.39
chronic fatigue syndrome*	Gardasil	74	2.41	32.32
	Cervarix	33	5.50	92.84
allergy	Cervarix	47	3.19	60.26
anaphylactoid reaction	Cervarix	11	12.14	66.68
appendicitis	Cervarix	10	5.52	28.22
encephalitis*	Cervarix	15	3.19	19.16
colitis ulcerative*	Cervarix	9	4.54	19.79
arthritis	Cervarix	72	14.62	501.12
juvenile idiopathic arthritis*	Cervarix	24	16.96	184.01
rheumatoid arthritis*	Cervarix	12	4.00	22.03
synovitis*	Cervarix	7	8.83	32.42
vasculitis*	Cervarix	8	2.72	7.53
lymphadenitis	Cervarix	8	2.67	7.24
Musculoskeletal or connective tissue AE				
cataplexy	Cervarix	9	3.61	14.13
fasciitis	Cervarix	7	15.45	50.48
arthralgia	Cervarix	217	2.07	111.16
joint effusion	Cervarix	8	6.42	26.87
joint swelling	Cervarix	28	2.04	13.44
hypertonia	Cervarix	13	7.18	49.17
hypotonia	Cervarix	30	2.57	25.27
clonus	Cervarix	7	2.63	6.16
convulsion	Gardasil	1211	3.14	832.63
	Cervarix	168	3.32	233.86
clonic convulsion	Cervarix	14	30.91	147.39
tonic convulsion	Cervarix	18	16.73	136.82
hypokinesia	Cervarix	8	2.94	8.81
muscular weakness	Cervarix	180	2.69	169.79
muscle spasms	Gardasil	481	2.04	147.53
muscle twitching	Gardasil 9	77	2.22	36.89
muscle rigidity	Gardasil 9	42	2.72	30.64
myoclonus	Cervarix	14	5.89	42.64
Nervous system AE				
hyporeflexia	Cervarix	6	2.65	5.36
autonomic nervous system imbalance	Gardasil	71	2.16	24.53
	Cervarix	46	8.93	215.62
encephalopathy*	Cervarix	17	10.35	90.64
narcolepsy	Cervarix	19	4.47	40.97
Guillain-Barre syndrome*	Cervarix	43	3.44	62.47
optic neuritis*	Cervarix	16	2.26	10.00
orthostatic intolerance	Gardasil	90	3.29	64.74
	Cervarix	61	11.22	348.27
postural orthostatic tachycardia syndrome*	Gardasil	236	6.65	328.21
peripheral neuropathy*	Cervarix	60	11.40	346.75
Prenatal, perinatal or neonatal disorder AE				
spontaneous abortion *	Gardasil	249	2.90	150.26
premature labor*	Gardasil	79	4.54	81.53
Reproductive system AE				
amenorrhoea*	Gardasil	180	9.36	301.74
menorrhagia	Gardasil	133	8.36	210.90
	Cervarix	15	2.70	13.99
menstrual disorder	Gardasil	130	5.76	163.62
	Cervarix	43	6.49	146.47
dysmenorrhoea	Gardasil	132	5.85	168.02
	Cervarix	45	7.16	170.16
menstruation delayed	Gardasil	85	12.09	158.16
menstruation irregular	Gardasil	201	6.04	261.92
	Cervarix	54	6.23	176.01
ovarian cyst*	Gardasil	68	6.57	93.64
vaginal hemorrhage*	Gardasil	81	2.31	32.35
	Cervarix	14	2.29	9.02
Respiratory system AE				
hyperventilation	Gardasil	169	2.26	64.96
	Cervarix	64	5.36	174.85
tachypnea	Cervarix	6	3.53	9.08
respiratory disorder	Cervarix	8	2.67	7.24
respiratory distress	Cervarix	8	2.77	7.83
Systematic AE				
general physical health deterioration	Gardasil	97	3.09	63.93
Tumor AE				
injection-site mass	Gardasil 9	74	2.32	39.09
Urinary system AE				
dysuria	Gardasil	100	3.30	72.20
genital hemorrhage	Cervarix	7	41.21	82.41
hematuria	Cervarix	11	5.71	32.35
metrorrhagia*	Cervarix	11	8.45	48.88
urinary retention	Cervarix	8	3.62	12.62
urinary tract infection*	Gardasil	138	3.01	87.77
urinary incontinence*	Gardasil 9	56	2.38	31.42

The top-level categories follow the Ontology of Adverse Events (OAE) hierarchy. AE: adverse event. *Serious adverse event (SAE).

(e.g., amenorrhoea and dysmenorrhoea). For Gardasil 9 (Figure S1b), three local AEs (i.e., injection site discharge, hypoaesthesia, and mass) commonly occurred in males, but rarely in females. In general, the AEs

associated with Gardasil more frequently occur in females than in males, while Gardasil 9 had the opposite profile.

3.3. SAEs mined and analysis by GPS in gender and age stratification

We directly downloaded the VAERS data during 2006–2020 and set gender/age stratifications in GPS algorithm to detect the SAEs related to the three HPV vaccines. By adopting the filtering criteria $EB_{05} \geq 2$, our study identified 29, 24 and 7 SAEs associated with Cervarix, Gardasil, and Gardasil 9, respectively, after GPS algorithm with gender stratification (Table 2), and we also found 17, 5, and 1 SAEs associated with Cervarix, Gardasil, and Gardasil 9, respectively, after GPS algorithm with age stratification (Table 2). Overall, 41 statistically significant unique SAEs were obtained by GPS methods, of which, 10 SAEs (i.e., premature menopause, autoimmune encephalitis, acute disseminated encephalomyelitis, thrombosis, pulmonary embolism, abortion, autoimmune thyroiditis, juvenile myoclonic epilepsy, myasthenia, and disability or permanent damage) were newly found since they were not included in the results of the Frequentist statistical methods.

For comparison, we also used the GPS models with gender/age stratification to recognize the association between these 41 SAEs with all other vaccines in VAERS. As shown in Figure 2, in gender stratification, the SAEs of postural orthostatic tachycardia syndrome and amenorrhoea had stronger association with the three HPV vaccines comparing to the other vaccines (e.g., Menomune and Dryvax) (Figure 2a and 2b); Gardasil and Gardasil 9 had stronger association with premature menopause (Figure 2c), Cervarix and Gardasil had stronger association with metrorrhagia (Figure 2d), Cervarix had stronger associations with the SAEs of autoimmune encephalopathy, autoimmune encephalitis, and juvenile idiopathic arthritis (Figure 2e, Figure 2f, and Figure 2g). In age stratification, Cervarix had stronger association with the SAEs of juvenile idiopathic arthritis and autoimmune encephalopathy (Figure 2h and Figure 2i).

At last, our study identified 34 Cervarix-specific SAEs, 26 Gardasil-specific SAEs, and 7 Gardasil 9-specific SAEs based on the Frequentist and Bayesian methods. Particularly, 4 SAEs (i.e., unconsciousness, syncope, postural orthostatic tachycardia syndrome, and amenorrhoea) were shared by all three vaccines. In total, 46 unique statistically significant SAEs were identified to be associated with at least one of these three vaccines. Figure S2 gives the OAE-based hierarchical structure of these SAEs, and these SAEs were enriched in the categories of *behavioral and neurological AE*, *immune system AE*, *nervous system AE*, and *reproductive system AE*.

4. Discussion

To the best of our knowledge, this study is the first to systematically compare and analyze the licensed HPV vaccine-associated AE profiles from the VAERS database based on the biomedical ontology methods. Compared to the existing narrative reviews, our ontology-based analysis provided the lists of significant AEs as well as allowed pathological classification to these AEs, leading to more specific insights for signal detection and hypothesis generation. In the following, we mainly discussed the safety insights of HPV vaccination from gender, age, dose schedule, and special significant SAEs.

4.1. Gender

Nowadays, more and more Gardasil and Gardasil 9 vaccine doses were administered to males because the male vaccination not only provides immune protection for males but also has a "herd effect" for females by preventing the HPV transmission [45]. Our study tried to assess differences in AE profiles between males and females, and to identify any evidence for AEs of special interests in different genders. For Gardasil, digestive system AEs and reproductive system AEs were more common in female than male recipients (Figure S1a). For Gardasil 9, the most

Table 2. Identified SAEs by GPS modeling with gender/age stratification.

Stratification	SAE	Vaccine	EB_{05}
gender	abortion*	Gardasil	2.60
gender	acute disseminated encephalomyelitis*	Cervarix	2.04
gender	Alopecia	Cervarix	2.27
gender		Gardasil	4.45
age			2.21
gender	amenorrhoea	Cervarix	2.84
gender		Gardasil	5.85
age			2.20
gender		Gardasil 9	2.77
gender	amnesia	Cervarix	3.00
		Gardasil	2.97
gender	anaphylactic shock	Cervarix	3.20
age			2.84
gender	autoimmune encephalitis*	Cervarix	2.80
gender	autoimmune encephalopathy	Cervarix	47.00
age			2.29
gender	autoimmune thyroiditis*	Gardasil	2.77
gender	chronic fatigue syndrome	Cervarix	13.70
age			3.43
gender		Gardasil	2.90
gender	circulatory collapse	Cervarix	3.65
age			2.34
gender	circulatory shock	Cervarix	10.85
age			10.40
gender	colitis ulcerative	Cervarix	2.61
		Gardasil	2.81
gender	disability or permanent damage*	Cervarix	2.06
gender	encephalitis	Cervarix	2.52
gender	encephalopathy	Cervarix	3.43
age			2.74
gender	epileptic seizure	Cervarix	5.33
age			2.94
gender		Gardasil	2.25
gender	Guillain-Barre syndrome	Cervarix	2.12
age			2.27
gender	juvenile idiopathic arthritis	Cervarix	20.51
age			4.57
gender	juvenile myoclonic epilepsy*	Gardasil	2.36
gender	metrorrhagia	Cervarix	13.96
age			2.62
gender		Gardasil	3.70
gender	myasthenia*	Gardasil	2.05
gender	neurogenic shock	Cervarix	2.93
gender	optic neuritis	Cervarix	2.53
gender	ovarian cyst	Gardasil	4.56
gender	peripheral neuropathy	Cervarix	6.69
age			5.87
gender	postural orthostatic tachycardia syndrome	Cervarix	6.12
gender		Gardasil	5.66
age			2.05
gender		Gardasil 9	3.23
gender	premature labor	Gardasil	3.45
age			2.08
gender	premature menopause*	Gardasil	4.31
		Gardasil 9	3.10
gender	pulmonary embolism*	Gardasil	3.12
age	rheumatoid arthritis	Cervarix	2.01
gender	schizophrenia	Cervarix	3.52

(*continued on next page*)

Table 2 (*continued*)

Stratification	SAE	Vaccine	EB_{05}
gender	seizure	Cervarix	4.47
age			2.27
gender		Gardasil 9	3.47
age			2.39
gender	spontaneous abortion	Cervarix	3.23
age			2.81
gender		Gardasil	2.79
age			2.33
gender	syncope	Cervarix	4.56
		Gardasil	4.31
		Gardasil 9	4.52
gender	systemic lupus erythematosus	Cervarix	5.43
age			3.08
gender		Gardasil	2.99
gender	thrombosis*	Gardasil	3.61
gender	unconsciousness	Cervarix	6.18
age			2.49
gender		Gardasil	2.98
gender		Gardasil 9	3.94
gender	urinary incontinence	Gardasil	2.19
		Gardasil 9	2.81
gender	vaginal hemorrhage	Cervarix	3.52
age			2.68
gender		Gardasil	2.30
gender	vasovagal syncope	Gardasil	4.56

* The SAE is new-found that not included in the results of the Frequentist statistical methods. SAE: serious adverse event.

common AEs were some injection-site symptoms that mild-to-moderate in intensity [13], and these AEs were more common experienced by males (Figure S1b). Furthermore, an updated review indicated that for vaccination with Gardasil 9, the rate of AEs was higher in younger females than younger males, and the rates were notably lower among older males [17]. Therefore, Gardasil 9 should be a preferred HPV vaccine for the male recipients, due to it has a reassuring safety profile.

4.2. Age

The three HPV vaccines have been recommended by FDA for vaccination in individuals 9 through 26 years of age [46, 47]. Of note, the FDA has extended the age range for the use of Gardasil 9 to peoples from 27 to 45 years of age in April 6, 2018 [48]. One objective of the study was to evaluate the AE profile of Gardasil 9 in all adults aged 27–45 years based on the VAERS data. We extracted 187 AEs case reports in the age group of 27–45 after vaccination with Gardasil 9, and obtained a mild AE profile with rare SAEs. A latest clinical study in European countries demonstrated that injection-site and vaccine-related systemic AEs were observed in women at 27–45 years of age, and no vaccine-related SAEs were reported [49]. These results support that the adults aged 27–45 years catch-up administered with Gardasil 9 not only is useful to prevent reinfection with HPV types encountered previously, but also is relatively safe.

4.3. Dose schedule

The three licensed HPV vaccines were originally trialled, evaluated, and recommended in a 3-dose schedule with doses spaced at 0, 1–2, and 6 months. In 2014, WHO recommended use of a routine 2-dose schedule in immunocompetent girls aged 14 and under, and following the United States changed their recommendation to 2-dose for those initiating the schedule before age 15 [50]. Indeed, an increasing body of evidence supported the comparable effectiveness of HPV vaccine despite a reduction of the doses number [51, 52, 53]. For instance, Markowitz et al. evaluated the prevalence of HPV types in US women aged 20–29 who were screened for cervical cancer, and analyzed their immunization status with the quadrivalent HPV vaccine: they could conclude that "among women who received their first dose at age ≤18, estimated HPV vaccine effectiveness was high regardless of number of doses." [53] Our study found that in VAERS case reports, many AEs (e.g., autonomic dysfunction syndrome) occurred after the vaccinees were immunized with the second or third dose of vaccine. Therefore, we have reasons to believe that the type and number of AEs will be reduced by reducing the dose schedule of HPV vaccination while the equivalent effectiveness of immunization can be provided [54].

4.4. Special significant SAEs

Most of vaccine-associated SAEs (e.g., acute encephalopathy after whole-cell pertussis vaccine and Guillain-Barré syndrome after seasonal influenza vaccine) have well-defined clinical manifestations [28, 55], they can be recorded accurately in VAERS database and classified appropriately through OAE hierarchies. However, there are some SAEs reported as being unpreventable or unexpected. For example, Poddighe et al. described a pseudo-neurological syndrome occurred shortly after the vaccination of Cervarix, but the patient showed no organic lesions [56]. Their diagnostic conclusion was a neuropsychiatric syndrome as no organic or electrophysiological lesion could be demonstrated. These SAEs are associated with medically unexplained syndromes, which make them cannot be defined and classified well. Although there is no sufficient evidence of certain causal relationship with these SAEs, a causal link with vaccine cannot be excluded in some individuals.

Autoimmune diseases are complex and multi-factorial disorders, and they are incurable and primarily rely on the drug control [57]. Thus, for the autoimmune AEs that occurred after vaccination, long-term and more refined classification follow-up studies are deserved. Previous studies have shown that there is a temporal association between HPV vaccination and autoimmune diseases due to the short-term increase in risk of autoimmune diseases after vaccination, but the causal relationship was unidentified [58, 59, 60]. Our study found several SAEs within autoimmune disorders were statistically significant with the HPV vaccines. In particular, Cervarix had stronger association with the autoimmune SAEs (e.g., autoimmune encephalopathy and juvenile idiopathic arthritis) in GPS models with gender/age stratification (Figure 2). Given that Cervarix is formulated with the AS04 adjuvant system [61], there is a theoretical concern that the use of the AS04 adjuvant may induce or aggravate underlying immune-mediated diseases [62].

Autoimmune encephalopathy and encephalitis are two new mined SAEs associated with the Cervarix vaccination. According to the direct effect of autoimmunity, autoimmune encephalopathy usually can be classified into two categories: rheumatic conditions with neuropsychiatric symptoms, and antibody associated autoimmune encephalitis [63]. Our study retrieved the detailed information for case report of every autoimmune encephalopathy or autoimmune encephalitis through the unique VAERS code. In general, some behavioral and neurological AEs like movement impairment, depression, and cognitive disorder have also been recorded in the case reports of autoimmune encephalopathy, and these AEs are consistent with the early psychiatric symptoms of autoimmune encephalopathy. In the case reports of autoimmune encephalitis, the most recognizable clinical syndrome is anti-N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis, which is a common form of autoimmune encephalitis [64]. In clinical practices, many patients suffered from autoimmune encephalopathy have made a good recovery when they were treated promptly [63, 64]. Therefore, it is important to carry out the early symptom surveillance including specific antibody detection for autoimmune encephalopathy.

We made a retrospective analysis for the detailed information of all autoimmune AE case reports, especially gender and medical history of

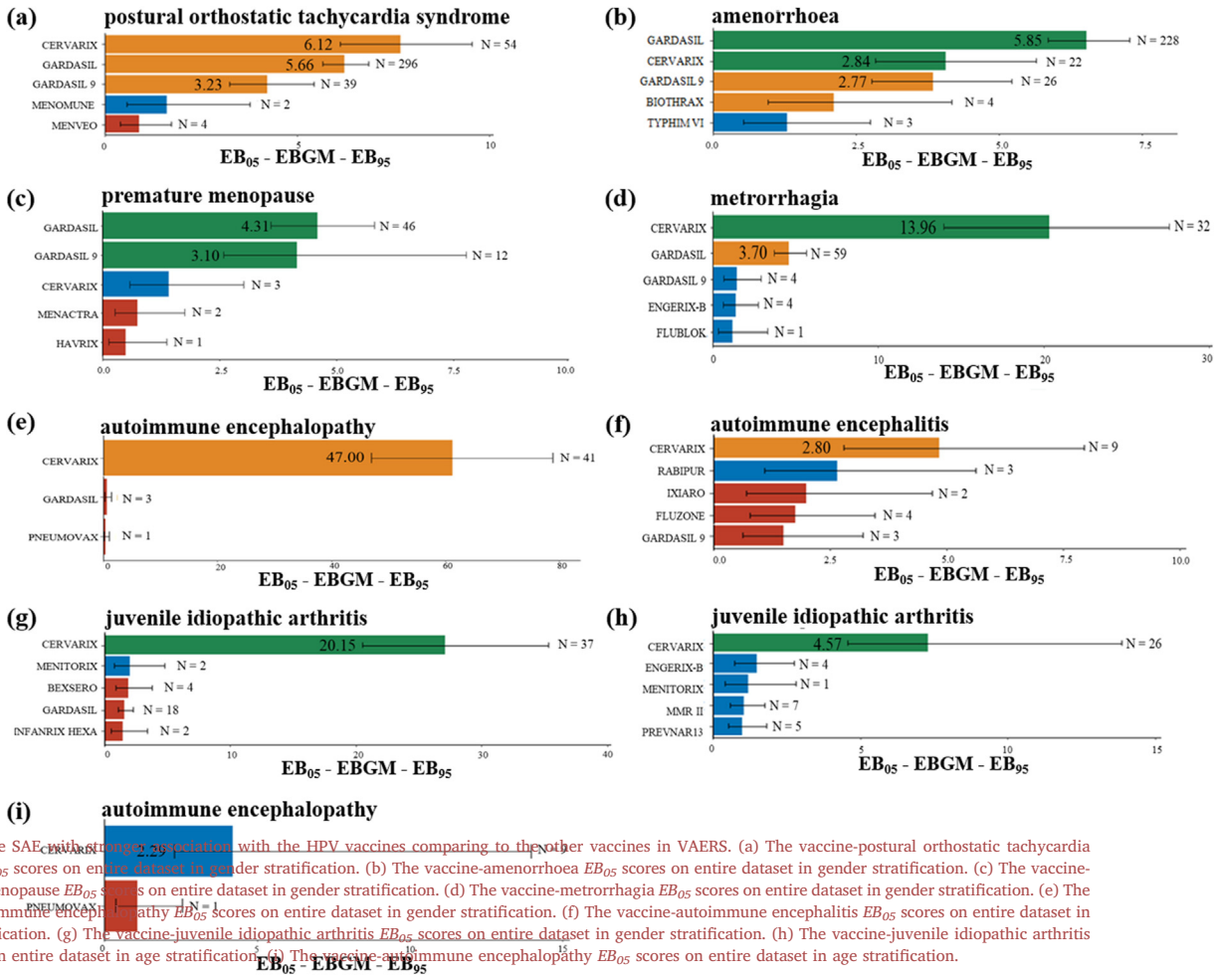

Figure 2. The SAE with stronger association with the HPV vaccines comparing to the other vaccines in VAERS. (a) The vaccine-postural orthostatic tachycardia syndrome EB_{05} scores on entire dataset in gender stratification. (b) The vaccine-amenorrhoea EB_{05} scores on entire dataset in gender stratification. (c) The vaccine-premature menopause EB_{05} scores on entire dataset in gender stratification. (d) The vaccine-metrorrhagia EB_{05} scores on entire dataset in gender stratification. (e) The vaccine-autoimmune encephalopathy EB_{05} scores on entire dataset in gender stratification. (f) The vaccine-autoimmune encephalitis EB_{05} scores on entire dataset in gender stratification. (g) The vaccine-juvenile idiopathic arthritis EB_{05} scores on entire dataset in gender stratification. (h) The vaccine-juvenile idiopathic arthritis EB_{05} scores on entire dataset in age stratification. (i) The vaccine-autoimmune encephalopathy EB_{05} scores on entire dataset in age stratification.

the vaccinee. The results showed that most of vaccinees who suffered from autoimmune AEs are females, and they were usually suffering autoimmune diseases during vaccination or had relevant medical histories before vaccination. For example, in the case reports of systemic lupus erythematosus AE after Gardasil vaccination (e.g., VAERS codes: 0340966, 0501783, 0677402, 0582178, and 0311261), the female recipients had suffered from lupus erythematosus disorders. In a systematic review, Quintero et al. indicated that females are more prone to develop autoimmune diseases because of hormonal changes as well as genetic factors [65]. Another study by Rojo-Contreras et al. found that there is a high prevalence of cervical HPV infection in Mexican women with autoimmune diseases (i.e., systemic lupus erythematosus and rheumatoid arthritis) [66]. In addition, several cases studies have reported that some autoimmune diseases developed or aggravated following HPV vaccination in the patients [59, 67, 68]. In light of the findings of the present and previous researches, we suggest that people with autoimmune disorders should actively consult their physicians and/or healthcare providers, and then make a decision for the catch-up immunization after assessing the potential risks of HPV vaccination.

The association between the HPV vaccination and syndromes with autonomic dysfunction has been evaluated in many studies [69, 70, 71, 72]. For example, Brinth et al. reported the characteristics of 35 women aged 23.3 ± 7.1 of years with the postural orthostatic tachycardia syndrome (POTS) starting in close relation to the Gardasil vaccination [69]. The POST and chronic fatigue syndrome (CFS) were identified in our study that have a temporal relation to the HPV vaccination, especially POTS performed stronger statistically significant with all the three HPV vaccines in GPS model with gender stratification comparing with all others in VAERS (Figure 2a). In some case reports of POST (e.g., VAERS codes: 0505884, 0506592, 0506598, 0506786, 0506795, and 0506797), the diagnostic results even stated that the temporal association between vaccination and the onset of symptoms of POTS in healthy young women is significant and deserves further investigation for assessment of a possible causal relationship.

At present, there is a general consensus that the POTS and CFS are heterogeneous disorders with uncertain etiology [73, 74]. They could individually have a wide range of unique presentations, and also considerable clinical overlap, such as headache, severe fatigue, and sleep disturbance [70]. In the hierarchy of OAE, the POTS and CFS were classified in the *nervous system AE* category as well as the *immune system AE* category by reasoning [21]. In vaccine administration, the CFS was considered as an autoimmune/inflammatory syndrome probably induced by adjuvants [75]. The studies on case reports suggested that there is an autoimmune etiology of POTS after HPV vaccination [71, 72]. Furthermore, Martinez-Lavin et al. proposed a general hypothesis that the vaccine-induced autoimmune dysautonomia is the common pathogenetic

mechanism for these symptoms of POTS and CFS [76]. In summary, we need to stay alert on that the POTS and CFS may occur following HPV vaccination in vaccinees, and correct diagnosis is essential for prompt and effective management of this condition.

The effect of the HPV vaccine on reproductive health is a major safety concern regarding HPV vaccination. Several studies have inverstigated the association between HPV vaccination and risk of pregnancy-related conditions. By a systematic review and meta-analysis, Tan et al. found that Cervarix vaccination during Pre-45 days to last menstrual period seemed to increase the risk of spontaneous abortion, and Gardasil 9 within 30 days of conception also seemed to increase the risk [77]. However, an observational long term follow-up of a randomized double blinded trial by Panagiotou et al. found no evidence that Cervarix vaccination affects the risk of miscarriage for pregnancies conceived for less than 90 days from vaccination [78]. Our study identified 8 SAEs of female reproductive health (i.e., abortion, premature baby, spontaneous abortion, amenorrhoea, vaginal haemorrhage, ovarian cyst, premature menopause, and metrorrhagia) statistically significantly associated with the three HPV vaccines (Figure S2). Specifically, amenorrhoea, premature menopause, and metrorrhagia performed stronger association with the HPV vaccines in GPS models with gender stratification comparing with all others in VAERS (Figure 2b, Figure 2c, and Figure 2d). The similar results have also been obtained in the post-licensure surveillance for HPV vaccination by Neha et al. [79].

Up to now, the association between HPV vaccination and related secondary reproductive conditions is still uncertain. Some studies have proposed that the possible mechanisms of the association between HPV vaccine and premature menopause (PM) may include HPV vaccine triggering autoimmune diseases to cause PM [58, 80], or the adjuvant aluminum in the vaccine inducing anti-ovarian positive antibody [81]. However, our results found a statistically signigicant association between HPV vaccination and adverse reproductive events, so a real association cannot be judged out [18, 82]. Thus, further researches for cauaslity investigation are necessary and urgent. Given all these, as recommended by the U.S. CDC, women who are in pregancy or prepare for pregnacy should preferably avoid the HPV vaccination.

5. Limitations

Some limitations in this study should be discussed. First, due to the inherent limitations of the VAERS data [83], the results obtained from this study cannot be used to ascertain the cause and effect relationships between the HPV vaccines and AEs. In future, population-based epidemiological studies and controlled clinical trials should be well-designed and conducted for detecting the real scenarios of specific AEs (especially for SAEs). Second, since the times to market and administered doses for the three licensed HPV vaccines are different, the associated AE statistical results may not be reasonable quantitative criteria for the security and efficacy of the specific vaccine. Third, while those peculiar or not well-defined SAEs may escape the OAE classification system of adverse events, there are likely to be some biases in our OAE-based AE profiles for the three HPV vaccines. Hence the term definitions and term hierarchies of OAE should be optimized constantly to improve efficiency in SAE classification and analysis.

6. Conclusions

In this study, we systematically investigated and analyzed the AE profiles associated with the three licensed HPV vaccines using the data from the VAERS database. Specifically, 169 statistically significant AEs as well as 46 unique SAEs were identified, and they were clustered in the OAE classification hierarchies related to behavioral and neurological conditions, immune system, nervous system, and reproductive system. Although the causal relationships between HPV vaccines and specific AEs cannot be established by current studies, the vaccine recipients, clinicians, and other stakeholders must be aware of the possibility of AEs (especially for SAEs) after immunization, and keep prepared of early interventions and timely treatments. Future studies should be conducted to further elucidate the causal association between HPV vaccines and associated AEs and to evaluate the potential biological mechanisms involved in these relationships.

Declarations

Author contribution statement

Wenrui Zi, Jiangan Xie: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Qiuyue Yang, Jun Su: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Yongqun He: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

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