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Safety profile assessment of HPV4 and HPV9 vaccines through the passive surveillance system of the Veneto Region (Italy) between 2008 and 2022: A 15-year retrospective observational study

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ABSTRACT

In Veneto Region, HPV vaccine has been actively offered to 12 year-old females since 2008, and to 12 year-old males since 2015. The study aims to analyze the safety profile of HPV4v and HPV9v vaccines and perform a case-by-case review of conditions of interest.

Spontaneous reports related to HPV uploaded to the database of the Regional Pharmacovigilance Center between 2008–2022 were included. HPV vaccine doses administered until April 2022 in the Veneto Region were considered to calculate the reporting rate (RR).

Potential "safety concerns" examined as conditions of interest were included through Standardized MedDRA or preferred terms searching queries. The level of diagnostic certainty was evaluated as per the Brighton Collaboration case definition criteria.

A total of 637 reports and 1316 Adverse Events Following Immunizations (AEFI) were retrieved: 469 for HPV4v (73.6 %) and 168 for HPV9v (26.4 %). Serious reports were 71 (11.1 %): 49 (10.4 %) for HPV4v and 22 (13.1 %) for HPV9v. The RR for serious events between 2008–2022 was 6.9/100,000 administered doses, with no differences by vaccine type. Females and adults showed higher overall RR compared to males and to children and adolescents ($p < 0.001$), this result was confirmed by stratifying analysis by vaccine type. One case of Guillain Barré syndrome, anaphylactic shock, thrombocytopenia, Henoch Schoenlein purpura and four generalized seizures were reviewed.

Vaccinovigilance data from the Veneto Region reaffirm a good safety profile for HPV vaccination and found no vaccine-related unexpected events. Such a detailed analysis may assist healthcare providers to advocate properly for HPV vaccination.

Abbreviations: AD, Administered Doses; AEFI, Adverse Events Following Immunizations; AIFA, Agenzia Italiana del Farmaco, the Italian Pharmacovigilance Authority Agency; CIN, Cervical intraepithelial neoplasia; CRPS, Complex Regional Pain Syndrome; DD, Doses Distributed; EMA, European Medicines Agency; GBS, Guillain-Barré syndrome; HIV, Human Immunodeficiency Virus; HPV, Human Papillomavirus; HPV2v, Bivalent HPV Vaccine; HPV4v, Quadrivalent HPV Vaccine; HPV9v, Nonavalent HPV Vaccine; HSP, Henoch Schoenlein Purpura; IME, Important Medical Events; MedDRA, Medical Dictionary for Regulatory Activities; POTS, Postural Orthostatic Tachycardia Syndrome; PT, Preferred Term; RNF, Rete Nazionale di Farmacovigilanza, the Italian Pharmacovigilance Network; RPC, Regional Pharmacovigilance Centers; RR, Reporting Rate; SMQ, Standardized Medical Queries; SPC, Summary of Product Characteristics; WHO, World Health Organization.

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1. Introduction

Human papillomavirus (HPV) infection accounts for 98 % of cervical cancer, the 4th most common female cancer in women aged 15 to 44 years in Italy, and it is a risk factor for the development of other cancers (e.g. anus, penis, vulva, vagina and head and neck cancers) along with genital warts[1,2]. Studies show that prophylactic vaccination programs not only have a great impact in reducing both the prevalence of low/high grade cervical lesions and HPV infection[3], but also lead to a further reduction of cervical cancers and cancer deaths compared to a secondary prevention with only HPV screening (Pap-test, HPV-DNA test) [4–6]. Thanks to the availability and effectiveness of HPV vaccination, in 2018 WHO implemented the "Global Strategy towards the Elimination of Cervical Cancer", one of whose targets is to have fully vaccinated 90 percent of 15-year-old girls by 2030, it represents the earliest worldwide cancer elimination strategy[7]. Further modeling studies confirmed that high HPV immunization and screening coverages may eliminate cervical cancer within 20 years[8].

Currently, three different preparations are available: a bivalent recombinant vaccine (HPV2v, 2007, types 16 and 18), a quadrivalent recombinant vaccine (HPV4v, 2006, types 6, 11, 16, 18) and a nonavalent recombinant vaccine (HPV9v, 2015, types 11, 16, 18, 31, 33, 45, 52, 58).

In the Veneto Region a free offer of the HPV4v vaccine to females born in 1996, twelve-year-old, was launched on January 1, 2008, with an active invitation to vaccination from the Local Health Units[9]; in the 2015 the same vaccination strategy has been extended to twelve-year-old males[10]. Currently, a free offer on request in the Veneto Region is also available for specific age groups as catch-up and for high-risk individuals. It is available for males born from 2001 until the age of 25 and for females born from 1996 until the age of 26. Are considered high-risk individuals: men who have sex with men, people living with HIV, women with cervical lesions at the CIN2 + stage, bone marrow transplant or solid organ transplant recipients individuals with hematological malignancies and those with chronic inflammatory autoimmune diseases[11–14].

Since 2017 the Veneto Region has begun offering the nonavalent HPV vaccine which is currently administered for routine immunization. In the latest National Vaccine Prevention Plan, the vaccine schedule envisages two doses at 0 and 6 months (up to 13 or 14 years of age), or three doses at 0, 1–2 and 6 months for older individuals[15]. Most of HPV vaccines are administered at the vaccination clinics of local health units. Vaccination coverage in 2020 in the Veneto Region for the first HPV dose for cohorts between 2004 and 2007 ranged from 69.3 % to 81.5 % in females and from 64.5 % to 75.0 % in males[16].

Several studies have been conducted on national passive surveillance databases to investigate the safety profile of HPV vaccines in the early years of the launch of vaccination campaigns[17–26]. Some adverse events, such as anaphylaxis or vasovagal syncope (occasionally associated to transient seizures-like events), had already been included in the Summary of Product Characteristics (SPC) of the drug after being observed in post-marketing surveillance[23,27–32]. In order to promote successful vaccination campaigns and ensure community adherence, it is essential to continue analyzing high quality passive surveillance data. Continuous surveillance is crucial to address safety concerns[33] and identify any unknown AEFI, which backs up the existing literature.

2. Aim

This study aims to analyze Italian Pharmacovigilance system reports following HPV4v and HPV9v vaccination in the Veneto Region and perform a detailed case review of conditions arising as potential safety concerns in literature.

3. Methods

3.1. Data source

3.1.1. Surveillance system

The Italian Pharmacovigilance system is based on spontaneous reports including multiple Adverse Events Following Immunization (AEFIs), collected through the Italian Pharmacovigilance Network (Rete Nazionale di Farmacovigilanza, RNF) coordinated by the Italian Medicine Agency (Agenzia Italiana del Farmaco, AIFA). Reports can be compiled spontaneously either by health professionals who become aware of an AEFI during their work, or by the general population, i.e. people who have experienced an AEFI.

AIFA, in collaboration with the Regional Pharmacovigilance Centres (RPCs), is responsible for post-marketing surveillance of drugs, including vaccines, in order to identify, assess and prevent adverse events. Furthermore, RPCs have to evaluate the possible causal relationship (causality assessment) between the vaccine and the AEFIs described in the serious reports.

3.1.2. Coding of adverse reactions

According to the European Medicines Agency's (EMA) Guidelines on Good Pharmacovigilance Practice, a serious report includes "any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect"[34,35]. Moreover, the reports may contain one or more adverse event, coded as Preferred Term (PT). Some of these PT could be part of the "IME list", a list of Important Medical Event (IME) Terms from the Medical Dictionary for Regulatory Activities (MedDRA), developed by EMA to aid the classification of suspected adverse reactions[36]. Although the presence of an IME in a report suggests a serious adverse event, the severity of the report still depends on the clinical course described and not solely on the associated IME.

The RPC of the Veneto Region evaluated the causal correlation of the individual reports in accordance with 2018 World Health Organization (WHO) criteria[37,38]: the causality assessment is either deemed "unclassifiable" (incomplete data make the report ineligible for causality assessment), "inconsistent" (available evidence excludes a causal relationship), "consistent" (available evidence confirms a causal relationship) or "indeterminate" (there is insufficient definitive evidence to support a causal relationship).

3.1.3. Administered doses

HPV Administered Doses (AD) per vaccine type, gender, age group, and year of administration between 01/01/2008 and 30/04/2022 were obtained from the vaccination registry of the Veneto Region.

3.2. Data analysis

3.2.1. Data analysis of overall reports

In this study all spontaneous reports following HPV4v and HPV9v vaccination loaded into the RNF databases for the Veneto region between 01/01/2008 and 30/04/2022 were included. Anonymized reports were categorized into sex, age group, year of administration, associated vaccines, PT, gravity assessment and causality assessment and were descriptively analyzed.

Frequency rates and percentages were used for categorical variables and means with standard deviations for continuous variables. A subanalysis was conducted on serious reports and IME terms.

Reporting Rate (RR) per subgroups were calculated between 2008–2022 as:

$$RR_i = \frac{Reports_i \times 100000}{AD_i}$$

Z-tests with Yates' continuity correction was used to compare proportion of adverse events (overall and serious) based on sex, age group and type of vaccine. A sub analysis stratifying by vaccine type was conducted to assess the effect of sex and age in the two populations receiving the HPV9v or the HPV4v. A p-value < 0.05 was considered significant. All analyses were performed using the R software (version 4.1.1)

3.2.2. Data analysis of conditions of interest

All included reports were evaluated to identify the occurrence of certain conditions of interest identified in the literature as potential vaccine "safety issue" (i.e. anaphylactic reaction, Guillain-Barré syndrome (GBS), thrombocytopenia, Henoch Schoenlein Purpura (HSP), generalized seizures, encephalitis/encephalomyelitis, Chronic Fatigue Syndrome (CFS), Postural Orthostatic Tachycardia Syndrome (POTS) and Complex Regional Pain Syndrome (CRPS))[23,26,34,39–41]. The searching strategy was based either on Standardized MedDRA Queries (SMQ) when available, or on a selection of PTs identified according to specified diagnostic criteria (see Appendix a). A case-by-case assessment to define the level of diagnostic certainty based on validated criteria (e.g. Brighton Collaboration case definition criteria when available, see Appendix 1) and an assessment of the causal link to immunization were then performed.

The Brighton Collaboration has developed standardized case definitions applied to specific diseases that increase the strength of vaccine surveillance analyses and provide a tool for reliable comparison of safety results from different passive surveillance systems. All reports scored as levels 5 ("not a case") were excluded from further analysis as well as all "unclassifiable" and "inconsistent" cases according to causality assessment (Appendix 1).

3.3. Ethical statement

The research was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and was approved by the Regional Centre for Pharmacovigilance of the Veneto Region (Italy).

4. Results

Between 2008 and 2022, a total of 637 reports and 1316 AEFIs (2.07 AEFIs per report) were retrieved in the Veneto Region and 1,024,418 HPV vaccine doses (HPV4v 63.93 %, HPV9v 36.07 %) were administered. Of all HPV4v vaccinations, 97.4 % were given until 2017, whereupon the quadrivalent preparation was replaced by HPV9v. Fig. 1 shows graphs on reporting rates per 100,000 AD per year.

The HPV9v RR was 45.5 over 100,000 AD and was significantly lower than the HPV4v RR (71.6/100,000AD) by 26.1 (0.95CI 16.5–35.8, $p < 0.001$). The female's overall RR was 69.0/100,000 AD and was significantly higher compared to males, the difference remained statistically significant even in the analysis stratified by vaccine type (Table 1, $p < 0.001$). The adult group showed higher overall RR (95.5/100,000AD), HPV9v RR (106.1/100,000AD) and HPV4v RR (98.5/100,000AD), then both children and adolescents (Table 1, $p < 0.001$). There were no significant differences in serious reports by vaccine type, sex, or age group (Table 1).

Table 2 shows the distribution of serious reports per seriousness criteria, causal relationship with the vaccination, outcomes, and reporting role over the whole sample and per vaccine type. Of all reports, 49 (10.4 %) and 22 (13.0 %) were classified as serious for HPV4v and HPV9v, respectively. No fatal reports were retrieved. RR for serious events was 6.9/100,000 AD for both vaccines, with 7.5/100,000 AD for HPV4v and 6/100,000 AD for HPV9v.

A total of 123PT were identified as IME (9.3 %), 89 (72.4 %) referred to HPV4v e 34 (27.6 %) HPV9v. The most reported conditions (based on PTs analysis), accounting for the 65,3% of all AEFIs retrieved are shown in Table 3. The most frequent conditions classified as serious in the IME list were hyperpyrexia, syncope/loss of consciousness, seizures, angioedema (representing 80 % of all retrieved IME), as shown in Appendix 2.

Adverse events described in literature as safety concerns, retrieved with MedDRA standardized algorithmic queries or searching selected terms, are summarized in Fig. 2. The retrieved cases of Chronic Fatigue Syndrome, Postural Orthostatic Tachycardia Syndrome, Complex Regional Pain Syndrome, encephalitis, encephalomyelitis and thrombocytopenia did not meet the inclusion criteria and therefore were not considered in the analysis (Fig. 2).

There was only one report of a potential GBS in a 11-years-old girl after 62 days from HPV4v vaccination. She had no pathognomonic electromyography and lumbar puncture, with no response to intravenous immunoglobulin therapy: she was discharged with a diagnosis of "suspected GBS under clinical investigation". The causality assessment was judged "indeterminate" due to lack of clear evidence for a causal link.

The retrieved case of anaphylactic shock, previously described as the life-threatening condition case, regards an 11-year-old girl who ten minutes after the second dose of HPV4v experienced a feeling of throat closure; she was treated with antihistamine and adrenaline, and she was admitted to the emergency room.

A potential case of HSP was found in an 11-year-old girl 17 days after HPV4v vaccination: she displayed petechiae, abdominal pain, myalgia.

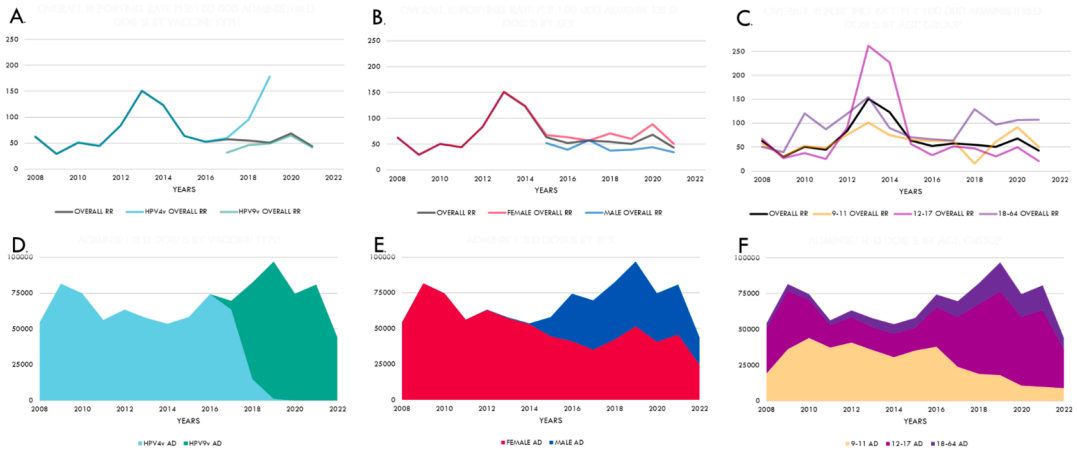


Fig. 1. A. Overall reporting rate per 100 000 administered doses by vaccine type. B. Overall reporting rate per 100 000 administered doses by sex. C. Overall reporting rate per 100 000 administered doses by age group. D. Administered doses by vaccine type. E. Administered doses by sex. F. Administered doses by age group.

Table 1
Reporting Rate (RR) of adverse events following immunization (AEFI) to HPV vaccines by vaccine type (HPV4 and HPV9), sex and age groups, and stratified by seriousness criteria (overall and serious). Children (9–11 year-old), Teens (12–17 year-old), Adults (≥18 year-old). RR was calculated over 100,000 administered doses (AD).

	HPV4 vaccine				HPV9 vaccine				HPV vaccine overall			
	Reports n (%)	AD	RR	p-Value	Reports n (%)	AD	RR	p-Value	Reports n (%)	AD	RR	p-Value
Overall	**469**	**654,942**	**71.6**		**168 (26.4)**	**369,476**	**45.5**		**637**	**1,024,418**	**62.2**	
Sex				0.043				<0.001				<0.001
Females	418 (89.1)	567,144	73.7		112 (66.7)	200,774	55.8		530 (83.3)	767,918	69.0	
Males	48 (10.2)	87,798	54.7		54 (32.1)	168,702	32.0		102 (16.0)	256,500	39.8	
Unknown	*3* (0.6)	87,798	54.7		2 (1.2)				5 (0.8)			
Age class				0.012				<0.001				<0.001
Children	219 (46.7)	339,028	64.6		29 (17.3)	68,631	42.2		248 (38.9)	407,659	60.8	
Teens	186 (39.6)	253,005	73.5		68 (40.5)	224,533	30.3		254 (39.9)	477,538	53.2	
Adults	62 (13.2)	62,909	98.5		81 (42.2)	76,312	106.1		133 (20.9)	139,221	95.5	
Unknown	2 (0.4)				0 (0.0)				2 (0.3)			
Serious	**49 (10.4)**	**654,942**	**7.5**		**22 (13.1)**	**369,476**	**6.0**		**71 (11.1)**	**1,024,418**	**6.9**	
Sex				0.212				0.219				0.843
Females	39 (79.6)	567,144	6.9		13 (59.1)	200,774	6.5		52 (73.2)	767,918	6.8	
Males	10 (20.4)	87,798	11.3		9 (40.9)	168,702	5.3		19 (26.8)	256,500	7.4	
Age class				0.342				0.224				0.618
Children	30 (61.2)	339,028	8.8		1 (4.5)	68,631	1.5		31 (43.7)	407,659	7.6	
Teens	14 (28.6)	253,005	5.5		15 (68.2)	224,533	6.7		29 (40.9)	477,538	6.1	
Adults	5 (10.2)	62,909	7.9		6 (27.3)	76,312			11 (15.5)	139,221		
Unknown	0 (0.0)				0 (0.0)				0 (0.0)			

Table 2
Focus on serious reports and percentage over total reports retrieved, stratified by seriousness criteria, causality assessment, outcomes and reporter role per HPV4v and HPV9v.

	HPV4v n (%)	HPV9v n (%)	HPV overall n (%)
Seriousness criteria			
Others clinically relevant events	23 (4.9)	14 (8.3)	37 (5.1)
Persistent or significant disability or incapacity	2 (0.4)	0 (0.0)	2 (0.3)
Hospitalization or prolonged hospitalization	23 (4.9)	8 (4.8)	31 (4.9)
Life-threatening condition	1 (0.2)	0 (0.0)	1 (0.2)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Causality assessment			
Consistent	31 (6.6)	18 (10.7)	49 (7.7)
Unclassifiable	2 (0.4)	0 (0.0)	2 (0.3)
Indeterminate	9 (1.9)	1 (0.6)	10 (1.6)
Inconsistent	7 (1.5)	3 (1.8)	10 (1.6)
Outcome			
Improvement	4 (0.9)	3 (1.8)	7 (1.1)
Not yet recovered	4 (0.9)	2 (1.2)	6 (0.9)
Full resolution	36 (7.7)	17 (10.1)	53 (8.3)
Resolution with sequelae	1 (0.2)	0 (0.0)	1 (0.2)
Not available	4 (0.9)	0 (0.0)	4 (0.6)
Reporter Role			
Other Health Care Provider	36 (7.7)	8 (4.8)	44 (6.9)
Physician	9 (1.9)	14 (8.3)	23 (3.6)
Patient or other not-health Care Provider	4 (0.9)	0 (0.0)	4 (0.6)
Pharmacist	0 (0.0)	0 (0.0)	0 (0.0)

She was admitted to the pediatric unit and discharged with a diagnosis of suspected HSP. The follow-up information was not available at the time of data collection. Causality assessment was judged to be "indeterminate".

Four cases of afebrile seizures occurred immediately after vaccination along with syncopal episodes (syncopal seizures), all of which were found to be "correlated" on causality assessment and resolved quickly. The two seizures cases classified as unrelated to the vaccination occurred more than a week after vaccination with, in one case, a confirmed underlying epilepsy disorder.

5. Discussion

Since rare events cannot be recovered by clinical trials because of their limited potency, surveillance on spontaneous reports on administered doses is fundamental. The analysis performed spans almost 15 years of surveillance in the Veneto Region: all reports for HPV vaccines were retrieved, which allows for a comprehensive evaluation.

The overall average RR of 62.1 reports per 100,000 AD was higher than those recorded in other similar studies[25,26,42] thanks to many reports for non-serious events. This highlight that the passive reporting system is well established with a positive awareness on AEFI reporting in the Veneto Region. Conversely, the overall RR for serious events (6.9/100,000 AD) closely mirrors the findings of earlier studies[21,22].

Nearly half of the severe cases were classified as serious due to hospitalization/long stay, which may, however, improperly include emergency room admissions without any subsequent hospitalization, distorting their estimate. The IMEs most frequently found in reports referred to expected adverse events (e.g., hyperpyrexia, decreased level/loss of consciousness, allergic reactions, and seizures) and without major consequences for the patient. In fact, most of the serious cases resolved completely or were improved at follow-up. In addition, the serious reports were not all causally related to vaccination, so the actual rate was even lower.

In our sample, there were more reports on HPV4v because the quadrivalent preparation was the only one available in the first decade of the immunization campaign. Since 2017, the latest updated version of the available vaccine, HPV9v, has rapidly supplanted the quadrivalent vaccine, leading to a subsequent decline in HPV4v-related reports. Comparing the number of reports by vaccine type, the average RR of the quadrivalent vaccine is significantly higher than the nonavalent one. This discrepancy may not only reflect an actual increase in HPV9v safety, but also a population more accustomed to HPV vaccination,

Table 3
Distribution by sex and vaccines type of the 10 most reported conditions (based on preferred terms analysis). Local reactions include at least one symptom such as pain, swelling, redness at the site of injection.

	Total (n = 637)	Female (n = 530)	Male (n = 103)	HPV4v (n = 464)	HPV9v (n = 168)
Reactions n (%)					
Local reaction	205 (32.18)	186 (35.09)	18 (17.48)	147 (31.34)	58 (34.52)
Hyperpyrexia/ Pyrexia	128 (20.09)	102 (19.25)	26 (25.24)	93 (19.83)	35 (20.83)
Headache	114 (17.90)	97 (18.30)	16 (15.53)	86 (18.34)	28 (16.67)
Urticaria	56 (8.79)	42 (7.92)	15 (14.56)	46 (9.81)	10 (5.95)
Presyncope/ Syncope/Loss of consciousness	56 (8.79)	43 (8.11)	11 (10.68)	41 (8.74)	15 (8.93)
Asthenia	47 (7.38)	36 (6.79)	11 (10.68)	31 (6.61)	16 (9.52)
Nausea	38 (5.97)	34 (6.42)	3 (2.91)	30 (6.40)	8 (4.76)
Erythema	36 (5.65)	30 (5.66)	5 (4.85)	30 (6.40)	6 (3.57)
Pain	31 (4.87)	22 (4.15)	9 (8.74)	19 (4.05)	12 (7.14)
Lymphadenopathy	28 (4.40)	22 (4.15)	6 (5.83)	12 (2.56)	16 (9.52)

	Female HPV4v (n=418)	Male HPV4v (n=48)	Female HPV9v (n=112)	Male HPV9v (n=54)
Reactions n (%)				
Local reaction	138 (33.01)	8 (16.67)	48 (42.86)	10 (18.52)
Hyperpyrexia/Pyrexia	81 (19.38)	12 (25)	21 (18.75)	14 (25.93)
Headache	77 (18.42)	8 (16.67)	20 (17.86)	8 (14.81)
Urticaria	36 (8.61)	6 (12.5)	6 (5.36)	9 (16.67)
Presyncope/Syncope/ Loss of consciousness	39 (9.33)	6 (12.5)	4 (3.57)	5 (9.26)
Asthenia	24 (5.74)	7 (14.58)	12 (10.71)	4 (7.41)
Nausea	28 (6.7)	2 (4.17)	6 (5.36)	1 (1.85)
Erythema	27 (6.46)	3 (6.25)	3 (2.68)	2 (3.7)
Pain	13 (3.11)	6 (12.5)	9 (8.04)	3 (5.56)
Lymphadenopathy	10 (2.39)	2 (4.17)	12 (10.71)	4 (7.41)

leading to fewer non-serious reports due to an increased perceived safety. Indeed, in support of the last hypothesis, there is no statistically significant difference between the overall RRs for serious events and the two vaccine types.

Data on reports from the male population came only from 2015 when the vaccination has been extended to them[10]. Although adults were not predominantly involved in the active vaccination campaign, the vaccine is available cost-free upon request for specific age groups and high-risk individuals, and on payment upon request for people outside these categories[11–15]. There was no significant difference in serious report RR based on sex or age group, while the overall RR was significantly higher in females and adults compared to males and both children and adolescents. These differences may be related to an actual higher burden of non-serious AEFIs in these groups or a different attitude of these populations towards AEFIs reporting, with women being shown to report more often than men[33,43].

Our results were mostly consistent with safety data from pre-licensure clinical trials, and no further signals were detected. The reports collected did not show any unexpected symptoms/conditions: most frequently reported AEFIs included local reactions and other general symptoms already known from the drugs SPC such as headache, pyrexia/hyperpyrexia, myalgia, or nausea[30,31]. This observation was consistent with available literature[21].

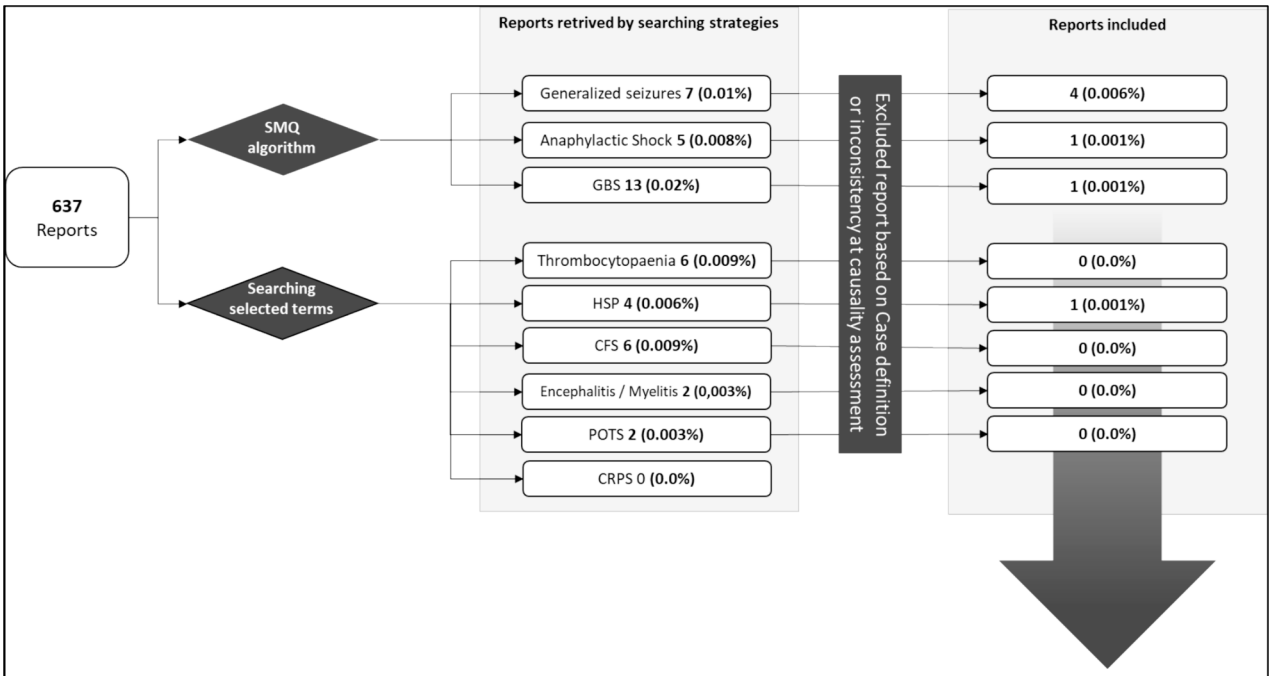
Studies have investigated cases of CRPS, CFS, POTS or encephalomyelitis/encephalitis noting that a proven association between some of these and HPV vaccines could not be established[24,39,40,44–49]. Indeed, in our study none of these "safety concerns'' was found that met the inclusion criteria: reports, retrieved through PTs attributable to such conditions, did not sufficiently meet the case definitions. Similarly, no further vaccinovigilance studies raised signals related to CFS, CRPS, or POTS[45–47] and the review conducted by EMA stated in 2016 that the available evidence does not support a causal association with HPV vaccination[48]. Cases of encephalomyelitis and encephalitis were absent as expected being the background incidence low[50]: in similar studies such reports are uncommon[24,49]; and even in a large cohort study the incidence rate was too low to compare vaccinated and unvaccinated populations[39]. No cases of thrombocytopenia consistent or indeterminate with the vaccination were found. This AEFI has been reported from other HPV4v post marketing surveillance studies and was included in the SPC of HPV4v with an unknown incidence rate because of its rarity[25] and two observational cohort studies found no association[41] and no significant increase of risk[54] with the vaccination.

One anaphylaxis case found was related to immunization with level a diagnostic certainty; five reports extracted with SMQ were found to be Brighton diagnostic certainty level 5, or "not a case". The RR for this recovered case was very low, approximately 0.15 case/100,000 AD, closely aligning with available literature at 0.1 case/100,000 doses distributed (DD)[26]. The case was promptly resolved without any lasting consequence on the patient, confirming the importance of proper training for early symptom recognition of symptoms and timely intervention.

The SPC of HPV4v and HPV9v include "syncope sometimes accompanied by tonic-clonic movements" as an uncommon potential adverse event. The occurrence of seizures after the initial loss of consciousness was detected by a passive surveillance study (2.6 per 100,000 DD) that referred to transient hypoxia due to the syncopal episode as a possible pathogenic mechanism of the tonic movements[28]. A registry-based cohort study conducted in Denmark and Sweden reported a significantly lower adjusted rate ratio for seizures in HPV4v-vaccinated adolescents than in unvaccinated adolescents (rate ratio = 0.66, 0.95CI 0.54–0.80)[40], while a U.S. analysis on the Vaccine Safety Datalink showed a comparable risk (relative risk = 1.02)[17]. Using the SMQ for generalized seizures, since among the criteria for diagnostic certainty the first was loss of consciousness following immunization, the RR was quite low in our study with a maximum of 0.45 cases per 100,000 AD in HPV4v and 0.27 in HPV9v which confirmed the rarity of the event. As for the occurrence of presyncope/syncope following HPV vaccination, it may represent an immunization stress-related response (e.g., anxiety) commonly observed among adolescents according to the literature, rather than a proper signal[51].

The only GBS case identified was classified as indeterminate and thus did not raise a safety signal. GBS is already a rare disease in the general population, with a background rate of incidence in Italy was 0.34 per 100,000 children aged 0–14 years and 0.57 per 100,000 adolescents/adults aged 15–34 years[52]. A large observational cohort study in France retrieved a higher risk of GBS among vaccinated female adolescents (incidence rate of 1.4 among exposed versus 0.4 per 100,000 person years among unexposed; adjusted HR = 3.78, 0.95CI 1.79–7.98)[42]. On the contrary, other studies showed it as an uncommon event [39]; and a retrospective ecological study conducted in Canada evidenced no increased risk of GBS related to HPV vaccination (OR = 0.81, 0.95CI 0.29–2.26)[53].

Regarding HSP, the possible case with level 2 diagnostic certainty was "indeterminate" because of insufficient information and possible other underlying clinical conditions. The few available data do not hypothesize an association between HPV vaccination and HSP. A retrospective cohort study on a large population of 18–44 women did not find any significant association (RR = 0.90, 0.95CI 0.46–1.79)[39]. Moreover, in another research, the incidence rate of HSP was lower in



Safety concerns	Vaccine type	Age (Years)	Sex	Brighton Criteria level	Causality assessment	Time of onset (days)	Outcome	Reporting Rate*
4 Generalized seizures	HPV4v=3 HPV9v=1	μ=12.5	all F	all level 1	all consistent	0	Full resolution	HPV4v=0.45 HPV9v=0.27
Anaphylactic shock	HPV4v=1	11	F	1	Consistent	0	Full resolution	HPV4v=0.15
Guillain Barrè Syndrome	HPV4v=1	11	F	4	Indeterminate	64	Improvement	HPV4v=0.15
Purpura of Henoch-Schoenlein	HPV4v=1	11	F	2	Indeterminate	17	Imprevement	HPV4v=0.15

Until April 2022 per 100 000 doses administered

Fig. 2. Flowchart showing the selection of included reports by applying the inclusion criteria. The table shows the characteristics of the final included reports for case analysis. GBS = Guillain Barré Syndrome; HSP = Henoch-Schönlein purpura; CFS = Chronic Fatigue Syndrome; POTS = Postural Tachycardia Syndrome; CRPS = Complex Regional Pain Syndrome; SMQ = Standardised MedDRA Queries.

vaccinated than in unvaccinated[41].

Finally, it is worth noting that in December 2022 the WHO recommended a one- or two-dose schedule for females aged 9 to 20 years, to give countries the opportunity to expand the number of girls who can be vaccinated, thus easing the burden on health systems. This recommendation was made out of the concern about declining HPV vaccine coverage globally and given the early data on the efficacy of a single-dose schedule[55].

6. Strengths and limitations

Spontaneous reporting systems have intrinsic limitations such as underreporting, the low quality and completeness of available information, the difficulty of establishing a definitive causal link between the vaccine and the AEFI. Moreover, it allows only to calculate the RR of the adverse event and not the actual incidence rates. Despite these limitations, passive surveillance data are a valuable source of information to detect potential safety signals.

In addition, the retrospective design and context-specific nature of the study provided data that could not be easily generalized, regional management and socio-cultural and demographic aspects being non-reproducible in other contexts. However, to the best of our knowledge, this is the first Italian study of HPV surveillance data collected at our regional level over a long period of time.

This study primarily includes data on quadrivalent vaccination in females as per the initial stance of the regional vaccine program. In the future, our data will cover more of the nonavalent vaccine safety profile in a more diversified population.

7. Conclusions

In the Veneto region, experience with the HPV vaccine has lasted almost fifteen years, with over one million doses administered. No safety issues have emerged for either HPV4v or HPV9v, and no proven association with rare and serious adverse events such as GBS, HSP, and others has been demonstrated. A similar analysis of Vaccinovigilance data was warranted in the future at cross-national level, with more reports, to evaluate the safety profile with HPV9v, now more widely used. Despite there were no concerning safety issues in the last 15-years of HPV vaccination, continuous monitoring of vaccines in the post-marketing phase (e.g., with passive surveillance) is a crucial element to detect early potential safety signals. It could also help to gather evidence to address hesitation promoting adherence to the vaccination program and building confidence in the safety of HPV vaccination.

Author contribution statements

In this work D. Dalla Valle, R. Benoni and F. Moretti conceptualized

and designed the study, made substantial contributions to original writing and were responsible for the data analysis. N. Soriolo and C. Battistella contributed to the interpretation of data and original writing. L. A. Gonella, M. Tonon and F. Da Re contributed to data collection and interpretation. S. Colpo and S. Montresor contributed to data collection. S. Tardivo and U. Moretti reviewed the study critically. G. Zanoni reviewed the study critically and contributed to data interpretation. All authors provided critical feedback and helped shape the research, analysis and contributed to the final manuscript.

Implication and contribution

A review of 637 Vaccinovigilance reports, with a detailed analysis of some potential "safety concerns", collected in the Veneto Region following HPV vaccines from 2008 to 2022 reaffirm a good safety profile. It is important to provide ongoing evidence on vaccine safety to promote vaccine adherence.

CRediT authorship contribution statement

Diana Dalla Valle: Writing – original draft, Data curation, Conceptualization. **Roberto Benoni:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Nicola Soriolo:** Writing – original draft. **Chiara Battistella:** Writing – review & editing, Conceptualization. **Francesca Moretti:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Laura Augusta Gonella:** Writing – review & editing. **Stefano Tardivo:** Supervision. **Silvia Colpo:** Writing – review & editing. **Sara Montresor:** Writing – original draft. **Francesca Russo:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Michele Tonon:** Writing – review & editing, Supervision. **Filippo Da Re:** Writing – review & editing, Data curation. **Ugo Moretti:** Writing – review & editing, Supervision. **Giovanna Zanoni:** Writing – review & editing, Supervision, Methodology, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2024.100511.

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