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EXPERT OPINION

Safety of human papillomavirus vaccines: a review

Michela Stillo, Paloma Carrillo Santisteve & Pier Luigi Lopalco†
ECDC, Stockholm, Sweden

Introduction: Between 2006 and 2009, two different human papillomavirus virus (HPV) vaccines were licensed for use: a quadrivalent (qHPVv) and a bivalent (bHPVv) vaccine. Since 2008, HPV vaccination programmes have been implemented in the majority of the industrialized countries. Since 2013, HPV vaccination has been part of the national programs of 66 countries including almost all countries in North America and Western Europe. Despite all the efforts made by individual countries, coverage rates are lower than expected. Vaccine safety represents one of the main concerns associated with the lack of acceptance of HPV vaccination both in the European Union/European Economic Area and elsewhere.

Areas covered: Safety data published on bivalent and quadrivalent HPV vaccines, both in pre-licensure and post-licensure phase, are reviewed.

Expert opinion: Based on the latest scientific evidence, both HPV vaccines seem to be safe. Nevertheless, public concern and rumors about adverse events (AE) represent an important barrier to overcome in order to increase vaccine coverage. Passive surveillance of AEs is an important tool for detecting safety signals, but it should be complemented by activities aimed at assessing the real cause of all suspect AEs. Improved vaccine safety surveillance is the first step for effective communication based on scientific evidence.

Keywords: adverse events, human papillomavirus, safety, vaccine

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1. Introduction

Human Papilloma Virus (HPV) causes around 26,800 cases of cancer and 15,000 deaths each year in the European Union/European Economic Area (EU/EEA) and around 27,000 cases and 6000 deaths in the US. Cervical cancer is the second most common type of cancer after breast cancer to affect women aged 15 – 44 years. The yearly incidence of cervical cancer per 100,000 females (all ages) ranges from less than 8.0 to 29.9, with the highest rates reported in the eastern EU Member States [1,2] while the US report an incidence of 7.9 per 100,000 females [3]. Two prophylactic HPV vaccines have been licensed, Gardasil® (Sanofi Pasteur MSD)/Silgard® (Merck Sharp & Dohme), a quadrivalent vaccine against the HPV types 6, 11, 16 and 18 (qHPVv) approved at the end of 2006 and Cervarix® (GlaxoSmithKline Biologicals), a bivalent vaccine approved in 2007 for immunization against HPV types 16 and 18 (bHPVv) [4]. Both vaccines contain non-infectious inactivated subunits, and protect against the high-risk HPV types 16 and 18, responsible for more than 70% of cervical cancer cases. The qHPVv also protects against HPV 6 and 11, which cause most cases of genital warts. In large Phase III trials, both vaccines have been shown to prevent more than 90% of precancerous lesions associated with types 16 or 18 among HPV-naive women.

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Article highlights.

- Both bivalent and quadrivalent vaccines are generally safe and well-tolerated.
- Site injection symptoms are the most frequent adverse events reported: of these, pain was generally the most frequently referred local symptom.
- Occurrence of serious adverse events was similar in both vaccine and control groups.
- No deaths from the introduction of the two vaccines have been attributed to human papilloma virus vaccination.
- Studies on the safety of the vaccine in some populations (men, women older than 25 years, HIV+ girls) have given satisfactory results.

This box summarizes key points contained in the article.

Despite the reassuring results on vaccine safety provided by large trials [5-7] and post-marketing studies [8-11], parental and girls anxiety regarding serious adverse events (AEs) and fear of unknown side effects are still barriers to vaccination [12]. In the US, parents safety concerns are the third ranked reason for non-adherence to the vaccination [13], and in Europe, lower rates of vaccine intentions are associated with misconception and fear of AE/SAE. Currently, the coverage rate with three doses is around 40% in the US [3] and ranges from 17 to 84% in EU/EEA, where few countries reach satisfactory coverage levels and vaccine programmes vary considerably in terms of vaccine type and target population [2].

The purpose of this review is to examine the most relevant and recent evidence on safety of HPV vaccines, including both severe and non-severe AEs.

2. Mechanism of action, clinical application and efficacy of HPV vaccines

Both vaccines contain antigens composed of L1 proteins specific to each HPV type, which are derived using recombinant technology and form non-infectious virus-like proteins (VLPs) [14].

The quadrivalent vaccine is an adjuvanted non-infectious recombinant vaccine prepared from the highly purified VLPs of the major capsid L1 protein of HPV types 6, 11, 16 and 18. The bivalent vaccine is an adjuvanted non-infectious recombinant vaccine prepared from the highly purified VLPs of the major capsid L1 protein of oncogenic HPV types 16 and 18 [15-18].

Since the VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease [9].

The HPV vaccines have been widely introduced in the national immunization programs in most of the worlds' medium- and high-income countries. Up to 2013, the vaccines were part of the national programs of 66 countries including almost all countries in North America and Western Europe [19] in schedules of three doses over a 6-month period [20]. During the same period, 25 of the 31 EU/EEA countries had implemented routine HPV vaccination programmes (ranging from 9 to 18 years) including catch-up programmes (range from 12 to 40 years) [21]. Both vaccines are widely used. Girls/women, especially pre-adolescent girls, are the main vaccination targets in almost all the countries where HPV vaccines have been introduced, only a few countries include males in their vaccination strategies. The main methods used to deliver the vaccines are school-based immunization, practice-based immunization, sexual and reproductive health clinics and other medical clinics (often used for catch-up programmes targeting older adolescents and women).

Although conceptually similar, quadrivalent and bivalent vaccines differ in several aspects, including in regards to their quantitative and qualitative composition, pharmaceutical form and posology (age at the time of first injection and immunization schedule). **Table 1** compares both vaccines, including the posology recommended by major regulatory bodies.

In terms of immunogenicity, bHPVv induces higher immune response when compared with qHPVv which may reflect the different adjuvant system used in each vaccine type [22].

The efficacy of both vaccines has been evaluated through pre- and post-licensure randomized control trials (RCT) [23]; the primary end point for these studies was prevention of CIN 2 or worse disease. The secondary efficacy end point was prevention of type-specific persistent infection, which is an obligate precursor of cervical cancer [24]. A recent review done by Schiller [25] showed that both vaccines are highly effective in preventing persistent infection and cervical diseases associated with vaccine-HPV types in young females.

Long-term protection of HPV vaccines, as well as for any new vaccine, is not fully predictable because of the short follow-up period (up to 9.3 years in the longest studies) and because it is not always related only to reasonable humoral immune response [26]; the persistence of immune response to bHPVv is reported in many studies [27,28] and in the summary of product characteristics, with a median follow-up period of 8.9 years and 100% seroconversion rate for HPV-16 and HPV-18 in the ELISA assay [29]. Protection up to 5 years post-vaccination has been demonstrated for qHPVv as well [30]. Long-term duration of efficacy (up to 6.4 years) reported in one of the efficacy studies suggests that antibody concentrations will remain high for at least 20 years [31] and some authors have developed mathematical models that suggest long-term immunity. Nevertheless, this still remains an ongoing and challenging issue [32].

A Phase III trial, including > 4000 males, suggests that prophylactic vaccination of boys and men with qHPVv may reduce the incidence of genital warts [33]. The study of Hillman *et al*. shows that immune responses to the qHPVv are broadly comparable in men and women [34].

Although the risk of acquisition of HPV infection is greatest in young and sexually active women, women older than

Table 1. Product information.

Name of the medicinal product	**Cervarix®**				**Gardasil®/Silgard®**			
Producer	GlaxoSmithKline Biologics				Sanofi Pasteur MSD/Merck Sharp & Dohme			
Qualitative and Quantitative composition	1 dose (0.5 ml) contains Human papillomavirus type 16 L1 protein Human papillomavirus type 18 L1 protein 2 adjuvanted by AS04 containing: 3-O-desacyl-4′- monophosphoryl lipid A (MPL) Adsorbed on aluminium hydroxide, hydrated (Al(OH)3)			20 micrograms 20 micrograms 50 micrograms 0.5 milligrams Al3+ in total	1 dose (0.5 ml) contains approximately Human papillomavirus type 6 L1 protein Human papillomavirus type 11 L1 protein Human papillomavirus type 16 L1 protein Human papillomavirus type 18 L1 protein Adsorbed on amorphous aluminium hydroxyphosphate sulfate adjuvant.			20 micrograms 40 micrograms 40 micrograms 20 micrograms 0.225 milligrams Al
Pharmaceutical form	Suspension for injection. Turbid white suspension.				Suspension for injection. After thorough agitation, it is a white, cloudy liquid			
Posology: age at the time of first injection and immunization schedule	**EMA** 9 to and including 14 years = Two doses each of 0.5 ml at 0, 6 months From 15 years and above = Three doses each of 0,5 ml at 0, 1, 6 months	**FDA** 9 – 25 years of age = Three doses each of 0.5 ml at 0, 1, 6 months	**TGA** Female from 10 – 45 years of age = Three doses each of 0.5 ml at 0, 1, 6 months	**PHAC** Recommended for females aged 9 – 26 years of age; may be administered to female over 26 years of age = Three doses each of 0.5 ml at 0, 1, 6 months	**EMA** 9 to and including 13 years of age = Two doses each of 0.5 ml at 0, 6 months From 14 years and above = Three doses each of 0,5 ml at 0, 2, 6, months	**FDA** 9 – 26 year of age = Three doses each of 0.5 ml at 0, 2, 6 months	**TGA** Females aged 9 – 45 years and males aged 9 – 26 years = Three doses each of 0.5 ml at 0,2,6 months	**PHAC** Recommended for: females aged 9 – 26 years of age, males between 9 and 26 years of age. May be administered to female over 26 years of age = Three doses each of 0.5 ml at 0, 2, 6 months
Method of administration	Intramuscular injection				Intramuscular injection			
Contraindications	Hypersensitivity to the active substances or to any of the excipients				Hypersensitivity to the active substances or to any of the excipients			

EMA: European medicines agency; FDA: US food and drug administration; PHAC: Public health agency of Canada; TGA: Australian government department of Health - therapeutic goods administration.

Table 2. Characteristics of Phase II/III randomized control trials included in Lu *et al*. [39].

	FUTURE I [104]	FUTURE II [46]	PATRICIA [105]	Muñoz [35]	Koutsky and Mao [106,107]	Harper [27]	Villa [30]
Vaccine	Gardasil®	Gardasil®	Cervarix®	Gardasil®	Cervarix®	Cervarix®	Gardasil®
Phase	III	III	III	III	III	III	II
Funding source	Merk	Merk	GlaxoSmithKline	Merk	Merk	GlaxoSmithKline	Merk
No. study sites	62	90	135	38	16	32	5
Countries included	16	13	14	7	1	3	5
Control	225 µg Aluminium hydroxyphosphate sulfate	225 µg Aluminium hydroxyphosphate sulfate	Hepatitis A vaccine	Placebo	Placebo	Placebo	Placebo
Age	16 – 24	15 – 26	15 – 25	24 – 45	16 – 25	15 – 25	16 – 23
	Case Control	Case Control	Case Control	Case Control	Case Control	Case Control	Case Control
	(2673) (2672)	(6019) (6031)	(9319) (9325)	(1908) (1902)	(1194) (1198)	(531) (538)	(272) (274)
Injection-related SAE	1 0	3 2	11 6	0 0	0 0	0 0	0 0
Risk ratio	3.0 (0.12,73.58)	1.50 (0.25,8.99)	1.83 (0.68,4.96)	Not estimable	Not estimable	Not estimable	Not estimable
SAE	48 45	45 54	701 699	3 7	4 3	22 19	2 2
Risk ratio	1.07 (0.71,1.60)	0.83 (0.56,1.24)	1.17 (0.64,2.14)	0.43 (0.11,1.65)	1.34 (0.30,5.96)	1.17 (0.64,2.14)	1.01 (0.91,1.09)

25 years are also vulnerable to new infections [35]. The use of qHPVv in women between 27 and 45 has been studied and a good level of protection against infection and disease from the HPV types contained in the vaccine has been found among those women who were not previously infected with those HPV types. The results of an international Phase III trial (VIVIANA), demonstrate that prophylactic administration of qHPVv to 24- to 45-year-old women is highly efficacious; furthermore, this study confirms that the vaccine is also highly effective in women with evidence of previous HPV 6/11/16/18 infection but with no evidence of current infection, which is consistent with data published in other studies [36].

3. Safety evaluation

Vaccines approved for use by the regulatory authorities have proven to be safe and effective. However, like other pharmaceutical products, vaccines are not completely risk-free and AEs will occasionally result from vaccination. Although most AEs are minor, in few cases more serious reactions may occur. As they are given to healthy individuals, a higher standard of safety is expected from immunizations as compared to other drugs [37]. To ensure continued public acceptance of vaccines and immunization programmes, it is essential to monitor the incidence of AEs following immunization (AEFI) [38]. For this review on the safety of the vaccines against HPV, we retrieved papers from PubMed® combining the concepts of HPV vaccine, safety and AEs in the search strategy. Results from seven RCTs from Lu *et al*. systematic review and meta-analysis are summarized in **Table 2** [39]. Papers retrieved which included reports from passive surveillance and reviews from the last 5 years, are summarized in **Tables 3** and **4**. All these studies have outcome measures that include AEs, including local and systemic AEs and serious AEs (SAEs), among which also chronic and/or autoimmune diseases (ADs) and death. Case reports and studies focused on a single AE are not displayed on the table. Some recent reviews with similar outcomes are also included [40-43].

3.1 Pre-licensure safety data

Vaccines, like other pharmaceutical products, undergo extensive testing, including safety, in three phases of clinical trials in human subjects before licensure. The review of Agorastos *et al*. [40]. assesses pre-licensure data from more than 60,000 women who received both vaccines, participating in different trials for establishing vaccine safety. Local reactions at the injection site (pain, redness and swelling) were significantly more frequent in vaccine than placebo recipients. Systemic AEFIs, including fever, nausea and dizziness were observed at a higher frequency than placebo. The most common systemic AEs following qHPVv vaccination reported in Resinger *et al*. study [44] were headache, fever and pharyngeal pain; however, there was no significant difference between vaccination groups and control groups. There were very few

Table 3. Human papilloma virus vaccines safety reviews.

Author	Title	Year of publication	Type of study	Place	Population	Vaccine type	Results	
							AE	SAE
Weber *et al*. [42]	Childhood vaccination-associated adverse events by sex: A literature review	2014	Review		12 studies	HPV16/18 and HPV6/11/16/18	The most frequent local adverse event was injection-site pain, the incidence of adverse events did not increase with increasing number of doses	No specific safety concern identified except for the Gee *et al*. [64] observation of an elevated risk of 1.98 for venous thromboembolism
Macartney *et al*. [41]	Safety of human papillomavirus vaccines: a review	2013	Review	/	/	HPV16/18 and HPV6/11/16/18	Injection-site adverse reaction (especially pain) and mild self-limited systemic symptoms (such as myalgia and headache) occur commonly after vaccination and should be anticipated. Some of these symptoms are more common in bHPVv	Consistent with the findings of the review no evidence supported an association of HPV vaccine with other outcomes, such new onset chronic diseases
Block *et al*. [43]	Clinical trial and post-licensure safety profile of a prophylactic Human Papillomavirus (types 6, 11, 16 and 18) L1 virus-like particle vaccine	2010	Review of five clinical trials	/	21,480 girls and boys	HPV6/11/16/18	Pain, the most common injection-site AE, occurred more frequently with vaccine (81% vaccine; 75% placebo aluminum; 45% placebo-saline). No differences were seen in the incidence of the most common non-serious AEs–headache and pyrexia	SAE occurred in 0.05% in vaccine group ad in 0.02% in placebo group. Of 18 deaths (0.1% vaccine; 0.1% placebo), all were considered unrelated to study treatment. New medical conditions which were potentially consistent with autoimmune phenomena were reported in 2.4% of both vaccine and placebo recipients
Agorastos *et al*. [40]	Safety of human papillomavirus (HPV) vaccines: A review of the international experience so far	2009	Review based on national and international agencies	US, Canada, Australia, Europe, Germany, France, UK		HPV6/11/16/18 and HPV16/18	Pre-licensure data: Injection site symptoms were the most reported symptoms in one of the studies they were reported more frequently in the vaccine group than in the control group. General symptoms was slightly higher in the vaccine group	Almost all the case-reports of SAE had weak or moderate strength of evidence for causality

AE: Adverse event; bHPVv: Bivalent HPV vaccine; SAE: Serious adverse event.

Table 4. Post-surveillance studies on human papilloma virus vaccines safety.

Author	Title	Year of publication	Type of study	Place	Population	Vaccine type	Results	
							AE	SAE
Angelo *et al.* [55]	Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme.	2014	Post-licensure passive surveillance	UK		HPV16/18	Ten most frequent AEs are non-serious AE and representing 86% of all reports	No specific safety concern identified from more than 4 years of HPV16/18 vaccine use in routine clinical practice
Markowitz *et al.* [10]	Human Papillomavirus Vaccination Recommendations of the advisory committee on immunization practices (ACIP)	2014	VAERS passive surveillance data	USA	18.083 person (male and female) for qHPVv and different pooled of safety analysis (from 12,000 to 57,323 females) for bHPVv	HPV16/18 and HPV6/11/16/18	qHPVv: Pain 83% of women and 61.4% men in vaccine group, 62% of women and 46.2% of men in control group. Systemic clinical AEs were reported by similar proportion of vaccine and control groups among both females and males. bHPVv: pain 91.9% in vaccine group and 76,5% in control group, redness 25.7% in vaccine group and 25.7% in control group, swelling 44.3% in vaccine group and 19.5% in control group. No differences were observed between the two groups for general symptoms	qHPVv: < 0.1% of person suffered serious AEs. bHPVv 5.3%in vaccine group and 5.9% in control group. New autoimmune disorder incidence was 0.8% in both groups. None of the deaths reported was considered to be vaccine-related
Harris *et al.* [68]	Adverse events following immunization in Ontario's female school-based HPV program	2014	Reports of confirmed AEs following immunization	Canada	Over the reporting period 691,994 vaccine doses were distributed	HPV6/11/16/18	213 HPV4 vaccine AEFI reports. In total there were 152 AEs associated with the 133 individual qHPVv vaccine AEFI reports. The majority of reports included a single AE (114/133; 86%) and the remaining included two or more distinct events (14%,19/133). The most frequently reported AEs were allergic reaction–dermatologic/mucosa' (25%), 'rash' (22%), and local/injection site reaction' (20%).	26% of reports had a non-specific event of 'other severe/unusual events' selected. Among 133 confirmed qHPVv vaccine AEFI reports, 7.5% (n = 10) were serious including two reports of anaphylaxis, two reports of seizure, one report of thrombocytopenia and one report of death (cardiac condition was responsible)

AE: Adverse event; AEFI: Adverse events following immunization; bHPVv: Bivalent HPV vaccine; qHPVv: Quadrivalent HPV vaccine; SAE: Serious adverse event.

Table 4. Post-surveillance studies on human papilloma virus vaccines safety (continued).

Author	Title	Year of publication	Type of study	Place	Population	Vaccine type	Results	
Levi *et al.* [60]	Evaluation of bivalent human papillomavirus (HPV) vaccine safety and tolerability in a sample of 25 year old Tuscan women	2013	Post marketing monitoring	Italy	271 participants	HPV16/18	The most frequently reported adverse reaction proved to be pain at the site of injection (83.4% of doses), followed by local swelling (20.8%) and pyrexia (14.6%).	No severe symptoms were registered.
Labadie [63]	Post licensure safety evaluation of human papillomavirus vaccine	2012	Passive surveillance from VigiBase, VAERS and RIVM databases	Global safety surveillance	/	HPV16/18 and HPV6/11/16/18	qHPVv: Syncope was the most reported symptom both in VARES (15%), in VigiBase the incidence was 12%. Local reaction was described in 14% of reports in VARES and 18% in VigiBase. bHPVv Local reaction were the most reported symptoms (16.2%) in RIVM and (12.8%) in VigiBase, followed by Syncope 8.7% in RIVM and 8.7% in Vigibase. Headache was frequently reported in VigiBase database: 21.1% of all reports	For all databases and for both vaccines SAE were reported in < 1% of cases, except for hypersensitivity reaction and urticaria that were between 1% and 4%, and Venus thromboembolic event that was reported in 1.5% of subjects who received bHPVv
Gold *et al.* [9]	Human papillomavirus vaccine safety in Australia: experience to date and issues for surveillance	2011	Surveillance	Australia	1394 reports of suspected AEFI on > 5.8 million doses of vaccine	HPV6/11/16/18	A total of 1394 suspected AEs following immunization (AEFI) have been reported. Most reports are of common and expected reactions.	Case series of more uncommon and serious AEs, both known to be potentially vaccine related (anaphylaxis, conversion disorders and lipoatrophy) and otherwise (multiple sclerosis and pancreatitis) have been published.

AE: Adverse event; AEFI: Adverse events following immunization; bHPVv: Bivalent HPV vaccine; qHPVv: Quadrivalent HPV vaccine; SAE: Serious adverse event.

Table 4. Post-surveillance studies on human papilloma virus vaccines safety (continued).

Author	Title	Year of publication	Type of study	Place	Population	Vaccine type	Results
Gee *et al.* [64]	Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink	2011	Prospective cohort study (prespecified AEs were selected based on safety data from prelicensure clinical trials)	US	600,558 females	HPV6/11/16/18	/
							No statistically significant increased risk for the outcomes studied (Guillan-Barre' syndrome, stroke, venous thromboembolism (VTE), appendicitis, seizures, syncope, allergic reaction and anaphylaxis. For venous thromboembolism an elevated risk of 1.98 among the youth could be observed.
Slade *et al.* [62]	Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine	2009	Post-licensure passive surveillance	US	More than 23 million doses distributed. 12,424 AEFI reports	HPV6/11/16/18	Most common local reaction reports included injection site pain (53%), erythema (28%) and swelling (22%). Syncope was the most frequent general SAE (74% of reports)
							Disproportional reporting of venous thromboembolic events was noted.

AE: Adverse event; AEFI: Adverse events following immunization; bHPVv: Bivalent HPV vaccine; qHPVv: Quadrivalent HPV vaccine; SAE: Serious adverse event.

serious vaccine-related AEs (< 0.1%), and they were no more frequent than in those receiving placebo. Another review with meta-analysis [45] including six clinical trials described similar results, demonstrating that, overall, the incidence of SAEs and deaths was balanced between the vaccine and control groups (odds ratio for SAEs 0.998, 95% CI 0.87 – 1.14; for death 0.91, 95% CI 0.39 – 2.14). In the study by Paavonen *et al.* [46]. on bHPVva subset of women completed and returned safety diary cards documenting symptoms experienced within the first 30 days after vaccination; injection site symptoms and symptoms such as fatigue, headache and myalgia were reported more frequently in the vaccine group than in the control group. The proportion of women reporting new onset chronic disease, AD, and significant medical conditions during the entire duration of the study was similar in both groups. Overall, all pre-licensure studies reported local and general symptoms to be higher in the HPV vaccine groups than in the placebo groups; however, most symptoms were transient. No differences were found regarding SAEs. In Rivera-Medina Phase III, observer-blind, multi-centre, randomized, parallel group, controlled study, the occurrence of SAEs was similar in both vaccine (1.1%) and control groups (1.3%); there was no difference between study groups in the occurrence of SAEs and no SAE in the bHPVv vaccine group was considered related to vaccination [47].

3.2 Post-licensure safety data

Vaccines continue to be monitored for safety after they are licensed. A range of surveillance options can be used to monitor the safety of vaccines and immunizations post-licensure [38]. Almost all countries have passive reporting systems for AEFI, where spontaneous events are reported by health care providers and consumers [41]. Examples of these passive reporting systems are vaccine adverse event reporting system (VAERS) in the US [48], the Canadian AE Following Immunisation Surveillance System (CAEFISS) [49], the UK Yellow Card scheme [50,51] or the Australian therapeutic goods administration system [52]; At the European level, there is no specific system to report AEFI, but vaccine safety reports are collected through the EUDRAVIGILANCE system at the EMA, as for any other drug AE. Additionally, spontaneous reports are also collected by law by the manufacturers using the MedDRA standard dictionary [8]. Even though passive reporting systems are the most widely used due to their relative ease of implementation, their cost and their ability to capture unexpected events, they are subject to reporting biases, such as under-reporting and/or stimulated reporting and above all they cannot prove causality.

On the other hand, active surveillance systems include large linked databases from defined populations (such as a single health care provider or Managed Care Organization) that were created separately from each other and linked to enable the sharing of data across platforms, like VigiBase™ created by the WHO [53] or the Vaccine Safety Datalink (VSD) project in the US [10,54]. Post-marketing studies, including

surveillance activities, are also useful to improve the ability to detect AEs that are not detected during pre-licensure trials through bigger vaccinated cohorts.

It is important to underscore that reported AEFIs include any untoward medical incident that take place after an immunization. Such reporting definitions are deliberately loose in order to improve reporting of events that may generate a safety signal. However, it is of utmost importance to further assess each event in order to prove or discount a causal relationship with the vaccine. Unfortunately, such investigation is often complicated by incomplete or scarce information; therefore, the causal relationship between vaccine and AEFI may turn out to be impossible to verify.

3.2.1 AEs

Local symptoms, which include pain, redness and swelling at the injection site, are the most frequent AEs reported for both vaccines also in the post-licensure phase [55]. Pain was usually the most frequently referred local symptom after each dose, often reported more frequently in people who were vaccinated with bHPVv compared to qHPVv, followed by redness and swelling; generally, the incidence of AEs did not increase with increasing number of doses [42,44,56]. In both vaccine and placebo groups, injection site symptoms were the most commonly reported, however, the incidence in vaccine groups is often significantly higher than in the control groups [10,47,57]. In Block *et al*. study [43], the proportion of individuals reporting an injection site AE was higher in qHPVv (82.9%) and aluminium-containing placebo recipients (77.4%) compared with non-aluminium-containing vaccine recipients (49%). Also in Resinger *et al*. study of qHPVv, the proportion of subjects who reported one or more injection-site or systemic adverse experiences tended to be higher after the first injection than after subsequent injections [58]. Local and general symptoms after bHPVv vaccination were found to be rare (< 5%) [47]. Additionally in their systematic review and meta-analysis, Lu *et al*. documented in detail the safety results of seven important RCT related to both vaccines [39]. Occurrence of AEs was reported in all RCT. Pain at injection site was the most frequently reported AE ranging from 83 to 93.4% in vaccine groups and 75.4 – 87.2% in control groups.

In the same and in other reviews, headache and fatigue were the most common vaccine-related systemic AEs [39,41]. Other general symptoms included headache, vasovagal syncope, fatigue, gastrointestinal symptoms, arthralgia, myalgia, rash, fever and urticaria, which are generally monitored by different types of surveillance systems after vaccination independently from the type of vaccine. Van Klooster *et al*. [59] found, in a post-marketing study conducted on over 1000 girls vaccinated with bHPVv, that myalgia was the systemic event most often reported, followed by fatigue and headache; the study also observed that older girls reported having myalgia, fatigue, listlessness, dizziness, nausea, sleeping problems, cough, shortness of breath and diarrhea after the first dose significantly more often than younger girls. Levi *et al*. [60] in a bHPVv post-licensure study described a statistically significant difference in the frequency of fever in their sample of 25 years old women when compared with a pre-adolescent group (14.6% against 3.3%, respectively). Klein *et al*. conducted a post-marketing retrospective observational study and observed a not unexpected association between qHPVv and syncope [61]. Also in the report from VAERS, Slade *et al*. described an increase of syncope events after qHPVv vaccination aggravated by falls and head injuries [62]. The study of Labadie *et al*. is a summary of post-licensure safety information from VigiBase, VAERS report on qHPVv and Rijksinstituut voor Volksgezondheiden Milieu (RIVM) report on bHPVv; vasovagal syncope is among the most frequently reported AEs in both VAERS and RIVM data [63]. On the other hand, in a recent Vaccine Safety Datalink study, the rates of syncope after qHPVv vaccination were comparable with those following health care visits for other vaccinations [64]. General symptoms like syncope are often associated with injection and for this reason could be prevented by the simple recommendation to have patients sit for 15 min after vaccination. Systemic clinical AEs were reported by Markowitz *et al*. in a similar proportion among both males and females who received qHPVv independently from their belonging to the group of vaccinated or to the control group [10].

3.2.2 SAEs

SAEs are generally defined as any medical occurrence that is life-threatening, requires or prolongs hospital admission, results in disability, incapacity or death [65,66]. ADs and death will be evaluated separately. The incidence of SAEs following bHPVv vaccination described in Schwartz *et al*. study was 7.1%. The most frequently reported SAEs were appendicitis, abdominal pain, incomplete spontaneous abortion and ovarian cyst. One fatal SAE was reported in a participant who experienced aortic rupture during a heart operation. None of the reported SAEs were considered by the investigators as related to vaccination [67]. Klein *et al*. studied a population-based cohort of 200,000 females, 44,000 of whom received all three doses of qHPVv; the findings from this large, comprehensive study did not detect any evidence of serious safety concerns secondary to qHPVv [61]. Harris *et al.* described an incidence of 7.5% (n = 10) SAEs following qHPVv vaccination, including reports of anaphylaxis, seizures, thrombocytopenia and a fatal case. Further review found that these reports were attributable to pre-existing conditions and no causal relation was attributable to the vaccine [68].

In the following paragraphs, we discuss specific events that have been studied more in depth in the literature as allegedly related or triggered by HPV vaccination.

3.2.2.1 Venous thromboembolism

In a 2011 prospective cohort study, an RR of 1.98 for venous thromboembolism (VTE) was observed among young girls (9 – 17 years) receiving at least one dose of qHPVv; all of five confirmed VTE cases were found to have other risk

factors for VTE; however, the study was unable to determine whether the VTE observed were attributable to these common risk factors, or of these were effect modifiers of the association between qHPVv vaccine and VTE [64]. In the post-licensure surveillance study from VAERS database of Slade *et al*., there were 56 reports of VTEs after qHPVv, for an RR of 0.2 case per 100,000 doses. Females may have other risk factors for VTE (contraceptive use, family risk, etc.). The population of young women who frequently use hormonal contraceptives overlaps with those receiving the qHPVv, and as such, coincidental occurrences of VTE among qHPVv recipients may be anticipated [62]. In a post-licensure study in Canada on qHPVv, no new cases of VTE were observed during the 4 years of the study duration suggesting no evidence of a safety concern for this outcome [68]. Finally, in two Scandinavian studies, the Arnheim-Dahlstrom study and the Scheller study, the rate ratio for the association between exposure to qHPVv vaccine and venous thromboembolism was 0.86 (95% CI, 0.55 – 1.36) and 0.77 (95% CI, 0.53 – 1.11), respectively; similarly, no association was observed in subgroup analyses by age, including only anticoagulant-treated cases, only exposed cases or when adjusting for oral contraceptive use. Therefore, studies did not identify safety signals with respect to venous thromboembolic events after the qHPVv had been administered [69,70].

3.2.2.2 Guillain–Barre' syndrome

Guillain–Barre's syndrome (GBS) is an acute inflammatory demyelinating polyneuropathy and has been alleged as one of the most common neurological SAE following different vaccines [71]; the occurrence of GBS after vaccination with qHPVv (Gardasil) has been investigated by many different authors; despite some studies describe a higher reporting rate of GBS in vaccinated girls [72,73], others report that the occurrence of GBS after HPV vaccination is not suggestive of a causal association [8,74,75]. Data from the Centre for Disease Prevention and Control (CDC), collected from the VAERS database, indicated that the reported number of cases was within the range expected by chance alone in the population [76]. In addition, the study of Gee *et al*. conducted a sequential analyses using data from VSD to detect any association between qHPVv exposure and pre-specified outcomes that included GBS, in addition historical background rate was used as the comparison group; a total of more than 600,000 doses were administered during the study and final conclusion was that there was no statistically increased between qHPVv and GBS [64]. In another large case-control study of young girls, 0 cases of GBS were observed in the qHPVv group [77].

3.2.2.3 Systemic lupus erythematous

Systemic lupus erythematous (SLE) is an AD, probably due to the pharmacological management of the disease with drugs like corticosteroids, patients with which have an increased risk of persistent HPV infection compared to healthy females [78]. They also have a higher risk for developing abnormal cervical smears and squamous intraepithelial lesions of the cervix. Because of these reasons, vaccination against HPV in lupus patients is especially important. Eight case reports in the literature suggested an association between vaccination and evolution and/or exacerbation of SLE; however, studies have not provided evidence in support of this association [79,80]. A prospective study with 27 SLE patients after qHPVv vaccination shows that this vaccine was generally safe, well-tolerated and immunogenic in SLE patients [81]. At the moment, all the evidence in the literature relates the suggestion that there might be a causal relationship between HPV vaccination and SLE exacerbation.

3.2.2.4 Other ADs

Concerns about autoimmune and neurological conditions being triggered by HPV vaccination may be fuelled by findings related to other vaccines. In the study of Arnheim-Dahlstrom [69], a significantly increased finding of three outcomes (Behcet's syndrome, Raynaud's disease, and type 1 diabetes) was observed, but further assessment showed no consistent evidence for a plausible causal association; first, these risk signals were relatively weak and, secondly, no temporal relation between vaccine exposure and outcome was evident. Nevertheless, these findings need to be investigated further in studies with longer follow-up time, validation of outcomes and data regarding time of onset. Case series of more autoimmune and uncommon diseases have been published, especially regarding demyelinating syndromes and other neurological events; some authors suggest that qHPVv is a potent immune-stimulatory signal that may trigger CNS disease in vulnerable populations, but subsequent evaluation using multiple epidemiologic methods did not demonstrate any association [9]. Furthermore, two large retrospective, observational cohort studies conducted with Kaiser Permanente on 189,629 females who received at least one qHPVv dose found that no one of autoimmune condition examined during the studies demonstrated any relation to vaccination timing, dose sequence or age [61,74]. The systematic case-control study of incidence of five types of ADs associated with qHPVv conducted by Grimaldi-Besonuda *et al*. in France, compared cases from a network of specialist centers with controls from a network of general practitioners, they found no evidence of an increase in the risk of the ADs following vaccination except for a lower Odds Ratio for central demyelination; however, also this finding had a low statistical power probably due to the rarity of AD cases [77].

3.2.2.5 Fatal outcome

In one review during 7.4 years follow-up, death was reported in < 0.06% among those who received bHPVv and 0.07% among the control group [10]. The bHPVv double-blind, randomized placebo-controlled trial conducted in China by Zhu *et al*. described no-differences in the incidence rates of death in vaccine group and in the control group [82]. In some

studies of AEFI cases associated with both vaccines reported by passive surveillance, no differences in death rates between the vaccines and the general population was observed [63]. Harris *et al*. observed all the qHPVv AEFI reports from 2007 to 2011 in Ontario with more than 600,000 doses of vaccine distributed; the only death that occurred was attributed to a pre-existing cardiac condition [68]. Deaths observed in the VAERS passive surveillance and reported by Slade *et al*. [62] described causes other than recent vaccination.

3.2.3 Safety in other population groups

3.2.3.1 Males

Gardasil is the only HPV vaccine licensed for males, for this reason, all the safety data are referred to this vaccine type. Studies which include the safety of the vaccine in male populations show that the most common AEs reported were injection-site related, and most of these were of mild-to-moderate severity [83]. Safety data for the US reported by the CDC [10] show that injection-site reactions are reported less in males than in women, for example, pain was reported in 61.4% of men and in 83.9% of women; vaccine-related SAE occurred in < 0.1% of vaccinated individuals. In the same report, the 3 years follow-up data showed that the same percentage of vaccinated (1.5%) and non-vaccinated men (1.5%) had conditions potentially indicative of autoimmune disorders, comparable to the prevalence in the general population (1.6%) [84].

3.2.3.2 Female aged > 25 years

Regarding safety in females aged more than 25 years, a Phase III RCT that randomly assigned women to receive either bHPVv or control (aluminium hydroxide) has shown that injection-site symptoms and general solicited symptoms during the 7-day post-vaccination period, occurred more often in the vaccine group than in the control group; other than these symptoms, the incidence of unsolicited symptoms, SAEs, new onset chronic disease and new-onset AD was similar in both groups. Furthermore, none of the deaths occurring during the study was due to vaccination [57]. Also, the qHPVv Munoz *et al*. case-control study shows that the proportion of women who reported SAEs after any vaccination was comparable between the vaccine and placebo. Injection-site AEs were mainly responsible for the slight increase in AEs recorded in the vaccine group [35]. No serious adverse experiences have been reported in the context of Luna *et al*. long-term study period as well [85].

3.2.3.3 Males and females HIV+

The prevalence of HPV and CIN 2/3 is higher in HIV-infected women than in uninfected women and varies over time and with the degree of immunosuppression [86]. HPV infections persist longer in HIV-infected women, and with increased immunosuppression, anogenital warts may become extensive and intraepithelial lesions are more likely to be dysplastic [87]. The incidence of anal cancer is increasing in HIV+ men, especially in men who have sex with men; furthermore, the risk of other HPV-associated cancers has been demonstrated to be increased among HIV-infected individuals [88]. A trial conducted by Levin *et al*. described the type and the frequency of AEs reported within 14 days after the first dose of qHPVv; AEs were infrequent and their occurrence was similar in vaccine and placebo recipients, except for injection site reactions ($p = 0.19$) that were more frequent in vaccine group. Injection-site reactions were mainly low grade and not more frequent after the second or third dose. AEs did not differ between groups [89]. Other studies report that vaccines are generally safe and well-tolerated both in pre- and post-licensing surveillance for HIV+ female and males [90]; in addition, results suggest that this population may benefit from HPV immunoprophylaxis [91,92]. Comparing the two vaccines, it should be noted that mild injection site reactions were more common in the group vaccinated with bHPVv, but the overall incidence of minor and major AE of both vaccines was acceptable for patients [93,94]. Further studies and trials are starting to enroll individuals to examine the long term efficacy of HPV vaccination in HIV-infected individuals [95].

3.3 Rumors on HPV vaccines safety

Since HPV vaccines have been introduced into national immunization programs, there have been a number of instances of public opinion being influenced by rumors of SAEs. Recently, more than 300 girls in Carmen de Bolivar (Colombia) were reported to have experienced fainting, shortness of breath and weakness in the limbs [96,97], allegedly linked to qHPVv. The cause of such mysterious event has not been fully explained, but the local authorities concluded that it was highly unlikely that there was any causal relationship with qHPVv and believe that it was a phenomenon of mass somatization disorder (hysterical neurosis). Nevertheless, such an event elicited strong attention from the media. Sudden deaths have been also allegedly connected to HPV vaccination. The majority of these reports have been disproved to have any causal relationship with the usage of the vaccine, such as in the UK where a girl from Coventry in 2009 died following a cervical cancer vaccination with claims of a causal association; but 2 days later medical evidence suggested that her death was due to a tumor heavily infiltrated in her chest [98,99]. Thanks to a good management of the event by public health authorities, such an event had a very limited impact on the HPV vaccination programme in the UK [100]. In contrast, when public health authorities have got little evidence on the real cause of the AE, the impact on the vaccination programme may be serious. In Spain, two girls apparently became ill after receiving one dose of qHPVv on the 4th and 6th of February 2009; as a consequence the Ministry of Health temporarily suspended the use of a batch of qHPVv. Despite the fact that the possibility of a correlation between the vaccine and the AE was subsequently excluded, in December 2009 the Ministry of Health received a petition signed by more than 9500 citizens who called for qHPVv withdrawal.

Similarly, in 2013, the Japanese government withdrew its recommendation for use of HPV vaccines in girls following public concerns about adverse effects [101]. In that occasion, the Japanese Ministry of Health instructed local health authorities not to promote the use of the vaccine until investigation on adverse effects was concluded; as a result HPV vaccine coverage was dramatically decreased [102].

4. Conclusion

This review has considered data on about the safety profile of two HPV prophylactic vaccines; most of the studies identified confirm the previous findings from pre- and post-licensure studies, according to which both vaccines are generally safe and well-tolerated. Site injection symptoms are the most frequent AEs reported, with pain being the most frequently referred local symptom after each dose, reaching an incidence of over 80%. These symptoms usually disappear shortly after vaccination and the incidence decreases with the second and third dose of vaccine. General symptoms such as headache, syncope and fever are reported from 10 to 30% of cases, although no significant difference has been observed between vaccination and control groups. The incidence of SAEs is variable but in most cases causal association is not proven. Additionally, the occurrence of these events is similar in both vaccine and control groups. For specific categories of SAE (ADs, venous thromboembolism, neurological syndromes) for which the absence of correlation with the vaccination has already been demonstrated, it is important to keep studying new cases to understand the pathogenesis of these diseases, especially when the reports come from passive surveillance where information to make this assessment may be missing. It is also of utmost importance to verify the absence of association between the vaccine and deaths which occurred after vaccination; no deaths from the introduction of the two vaccines have been attributed to HPV vaccination, but some cases have been poorly investigated leaving room for speculation, which could damage vaccination programs. Some studies on the safety of the vaccine in groups other than the primary target population (men, women older than 25 years, HIV+ girls) have already been published and have given satisfactory results comparable with those in the primary target population; recruitment for new trials is already started.

5. Expert opinion

Prevention of cervical cancer and other diseases associated to HPV infection is a public health priority. The positive public health impact of HPV vaccination depends on vaccine acceptance in order to reach high vaccination coverage. This is the reason why it is important to correctly manage any rumor about vaccine safety. Since 2008, when mass vaccination campaigns started in many industrialized countries, several SAEs allegedly reported as caused by HPV vaccines have been shown to be only temporarily associated but not causally associated, with the vaccination. Nevertheless, such events elicited large attention by the media and, in many cases, negatively impacted on the vaccination programmes due to concern in the public. The routine passive surveillance systems need to be reinforced in order to be able to identify any safety signal, but also a strong effort is necessary afterwards to improve the quality of AE investigation for causality assessment in order to better inform the communication by public health authorities.

A second generation of HPV vaccines might be available soon; these vaccines would be cheaper and more stable, able to protect against different and more numerous cancer-related strains and both therapeutic and prophylactic. Phase II and Phase III trials are now conducting by the manufacturers [103]. Improvement of safety profile, especially related to local reactogenicity, would be welcome in order to improve public acceptance.

A two doses schedule has been recently adopted in some countries and is under consideration by public health authorities in other countries. When the current three doses schedule will be progressively replaced by the two doses, consequently the overall acceptance of the vaccination programme may improve as well.

Both HPV vaccines available are generally safe and well tolerated. Efforts should be made to increase the vaccination coverage of these vaccines as an important tool to decrease the disease burden of HPV.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Affiliation

Michela Stillo[1], Paloma Carrillo Santisteve[2] & Pier Luigi Lopalco[†2]
[†]Author for correspondence
[1]Department of Public Health and Paediatric sciences, University of Turin
[2]ECDC, Stockholm, Sweden
E-mail: pierluigi.lopalco@ecdc.europa.eu