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Review

On the relationship between human papilloma virus vaccine and autoimmune diseases

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ABSTRACT

The human papilloma virus (HPV) vaccines were introduced to reduce the incidence of cervical cancer. The bivalent vaccine is effective against HPV-16, -18, -31, -33 and -45 while the quadrivalent vaccine is effective against HPV-16, 18, 31, 6 and 11 types. The immunisation, recommended for adolescent females, has led to high vaccine coverage in many countries.

Along with the introduction of the HPV vaccines, several cases of onset or exacerbations of autoimmune diseases following the vaccine shot have been reported in the literature and pharmacovigilance databases, triggering concerns about its safety. This vaccination programme, however, has been introduced in a population that is at high risk for the onset of autoimmune diseases, making it difficult to assess the role of HPV vaccine in these cases and no conclusive studies have been reported thus far.

We have thus analysed and reviewed comprehensively all case reports and studies dealing with either the onset of an autoimmune disease in vaccinated subject or the safety in patients with autoimmune diseases to define the role of the HPV vaccines in these diseases and hence its safety. A solid evidence of causal relationship was provided in few cases in the examined studies, and the risk vs. benefit of vaccination is still to be solved. The on-going vigilance for the safety of this vaccine remains thus of paramount importance.

Contents

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1. Introduction

The infection by specific oncogenic serotypes of human papilloma virus (HPV) represents a key step in the pathogenesis of cervical cancers as well as ano-genital and some other non-genital malignancies [1–5]. These diseases have a high impact on public health, with cervical cancer representing the fourth most common cause of cancer-related death worldwide, although the vast majority of these deaths (88%) occurs in developing countries.

The high burden of this disease in developing countries is caused mainly by the lack of screening and treatment facilities as well as suboptimal nutrition and hygiene [6]. As the evolution from infection to invasive cancer is slow, countries with screening programmes witness a reduced incidence of cervical cancer from a rate of 50–80/100,000 observed in unscreened women to a rate of 4–8/100,000 [1,3].

According to the Finland cancer registry, cervical cancer has declined of about 75% over the past 60 years, primarily because at least 70% of the population participates into a continuous Pap screening programme [2]. The importance of cervical cancer screening is remarkable, as when 20–29 year old unvaccinated women stopped attending Pap screening, a four-fold increase in cervical cancer occurred within five years from screening cessation [2,7,8].

Along with pap screening two vaccines were developed to protect against the infection of the two serotypes most commonly related to cervical cancer [1–3,9,10]. These vaccines have different formulation as the bivalent vaccine contains 20 μg each of HPV 16 and HPV 18 L1 proteins, while the quadrivalent vaccine contains 40 μg of HPV 16, 20 μg of HPV 18, 20 μg of HPV 6 and 40 μg of HPV 11 [9,11]. The protection of quadrivalent vaccine against HPV 6 and 11 is meant to prevent the occurrence of genital warts, a minor issue in patients without HIV, and respiratory papillomatosis [9].

The protection offered by these two vaccines extends to persistent HPV 31 infection, while only the bivalent vaccine could prevent persistent infections also from HPV 45 and 33 types [1,3,7].

Considerations on the clinical efficacy of these vaccines should take into account several important "real-world" factors including: efficacy against oncogenic HPV strains not covered by the vaccine and possibility of increased frequency of infections with these types; efficacy in women acquiring multiple HPV types; and effects in women with pre-existing HPV infections [12]. Although the results from clinical trials showed >97% HPV vaccine efficacy against HPV-16 and 18 related CIN-2/3 precancerous lesions, the corresponding figures against CIN-2/3 lesions caused by all high-risk HPV types associated with cervical cancer were only 16.9% in the per-protocol population. Thus, most likely, the true HPV vaccine efficacy lies somewhere between 16.9% and 70% [13].

A recent analysis found an increased cervical cancer incidence when vaccination was not accompanied by appropriate screening programmes [1,7,8], and that combining screening with vaccination does not significantly lower the incidence, while decreasing the number of women with abnormal screening tests [1].

In this view, it is important to better define the safety profile of HPV vaccines, especially considering their possible role as triggers of autoimmune diseases. Such definition is of paramount importance, as would allow physicians to provide a full and open discussion guiding women to make a decision for their cervical cancer protection [1]. In addition the introduction of a new vaccine in a population always raises concerns in terms of safety [14,15]. As expected based on previous experience with the introduction of other vaccines in a large cohorts of adolescent, several cases of adverse drug reactions have been reported also for the HPV vaccines, some of which being autoimmune diseases [16].

Numerous reports have thus raised the possibility of a causal relationship between vaccination and autoimmune diseases and hence on vaccine safety, without however providing a conclusive answer [15–19].

In this view, we have reviewed all available information on HPV vaccine safety in patients with autoimmune diseases and about the risk for healthy subjects to develop an autoimmune disease after vaccination; we provide an updated indication about the possible side effect of these vaccines.

2. Autoimmune diseases

2.1. Method of analysis

We carried out a PubMed search up to 2013 using the terms: "Autoimmune disease" OR "Multiple sclerosis" OR "Systemic lupus erythematosus" OR "Guillain–Barré syndrome" OR "Acute disseminated encephalomyelitis" OR "Demyelinating diseases" OR "Rheumatoid arthritis" OR "Juvenile idiopathic arthritis" OR "Inflammatory bowel disease" OR "Primary ovarian failure" AND HPV vaccine. We considered studies that included case reports and series, case–control studies, post-marketing surveillance programmes and published analyses by the Vaccine Adverse Event Reporting System (VAERS), a US-based national vaccine safety surveillance programme. We carried out an initial screening by reading each abstract to identify the articles meeting these inclusion criteria, which were conclusively assessed after a thorough analysis of their content. The retrieved studies were then entirety read to assess appropriateness. Citations from each included articles were examined in order to identify any other published study potentially meeting inclusion criteria. We limited the research to article written in English.

2.2. Acute disseminated encephalomyelitis (ADEM) and other demyelinating diseases of the central nervous system

Acute disseminated encephalomyelitis is classically described as a monophasic demyelinating disease of the central nervous system that typically follows an infection or, with a lower frequency, a vaccination. As highlighted in Table 1 numerous cases have been reported in the literature [20–24].

In most of the patients described in these reports, the pathology onset occurred within few days after the second or third vaccine shot [20–24]. The therapy response was generally good in all cases and no fatalities due to this condition were described [20–24].

ADEM following vaccination is a clinical entity poorly described in terms of epidemiological features [25]. Based on the reports to the VAERS and the European adverse event database, we recently showed that HPV vaccine is amongst the ones most commonly related to ADEM reports [25].

The incidence of ADEM following immunisation with the HPV vaccine is unknown, but the reporting rate was estimated to be $0.26/10^6$ (CI 95%: $0.16/10^6$–$0.37/10^6$) [23]. Such estimation was achieved considering the reports to the VAERS database and the doses of vaccine distributed in the same period [23].

Along with ADEM, other diseases characterised by demyelination of the central nervous systems have been reported. In a recent case series, Menge et al. reported on four cases of Neuromyelitis optica having occurred after the administration of HPV vaccine [26]. This disease is rarely observed in adolescent, but the observed cases may reflect the natural disease prevalence considering the large population exposed

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Table 1
Cases of autoimmune disease following HPV vaccination.

Ref	Authors	Vaccine	Condition	Age (years)
[20]	Shaffer et al.	Bivalent	ADEM	15
[21]	Wildeman et al.	Quadrivalent	ADEM	20
[22]	Mendoza et al.	Quadrivalent	ADEM	15
[23]	Pellegrino et al.	Quadrivalent	ADEM	13
[23]		Unknown	ADEM	12
[24]	Dimario et al.	Quadrivalent	ADEM	16
[26]	Menge et al.	Quadrivalent	NMO	17
[26]		Quadrivalent	NMO	14
[26]		Quadrivalent	NMO	13
[26]		Quadrivalent	NMO	18
[31]	Sutton et al.	Quadrivalent	CIS	21
[31]		Quadrivalent	CIS	16
[31]		Quadrivalent	CDMS	25
[31]		Quadrivalent	CDMS	21
[31]		Quadrivalent	CDMS	26
[32]	Change et al.	Quadrivalent	CIS	19
[32]		Quadrivalent	CIS	18
[40]	Gatto et al.	Quadrivalent	SLE	32
[40]		Quadrivalent	SLE	29
[40]		Quadrivalent	SLE-like	16
[40]		Quadrivalent	antiphospholipid antibody syndrome	16
[40]		Quadrivalent	SLE	19
[40]		Quadrivalent	SLE	13
[41]	Soldevilla et al.	Unknown	SLE	17
[41]		Unknown	SLE	45
[41]		Unknown	SLE	58
[53]	Colafrancesco	Quadrivalent	POF	14
[53]	et al.	Quadrivalent	POF	13
[53]		Quadrivalent	POF	31
[54]	Little et al.	Quadrivalent	POF	16
[55]	Cerami et al.	Quadrivalent	Autoimmune neuromyotonia	32
[56]	Della Corte et al.	Bivalent	Autoimmune hepatitis type 2	11
[58]	Melo Gomes et al.	Unknown	HSP	15
[58]		Unknown	Cutaneous vasculitis	13
[59]	Watanabe et al.	Unknown	Kikuchi–Fujimoto disease	14
[60]	Yonee et al.	Bivalent	Acute cerebellar ataxia	12
[61]	Katoulis et al.	Quadrivalent	Erythema multiforme	19
[62]	Pugnet et al.	Quadrivalent	Immune thrombocytopenic purpura	16

ADEM: acute disseminated encephalomyelitis; NMO: neuromyelitis optica; CIS: clinical isolated syndrome; CDMS: clinical defined multiple sclerosis; SLE: systemic lupus erythematosus; POF: primary ovarian failure.

to the vaccine [27,28]. It is therefore possible that these cases are simply close in time with the HPV vaccination rather than result from it [28].

2.3. Multiple sclerosis (MS)

The possible relationship between Multiple Sclerosis (MS) and vaccination in adolescent was described in the early 1990 following the large scale implementation of the immunisation programme with the Hepatitis B vaccine (HBV) [29]. The results of further studies failed to demonstrate a significant association between the HBV vaccine and MS, but the concerns about this possible association resulted in a massive loss of public confidence for this vaccine and in a low level of vaccine coverage [30]. Along with the introduction of the HPV vaccine, the onset or exacerbation of MS has been reported in some patients within few days from the vaccine shot [31,32]. Despite the coincidence in time between vaccine shot and disease onset, it is unclear whether the vaccination had a role in the onset of the disease. The reporting rate of MS following HPV vaccination, estimated as previously described for ADEM, was 0.08/100,000 doses in the United States and 0.14/100,000 doses in Australia. This reporting rate should be read considering the incidence of MS in the population exposed to the HPV vaccine [33], estimated to be one case per 100,000 subject every 6 weeks [15]. Such disproportion between the reporting rate and the incidence may indicate an absence of correlation between HPV vaccine and MS [15,33]. The possibility of a time coincidence between vaccine and disease onset is sustained by the relative high incidence of MS in the subject who received the HPV vaccine [33].

2.4. Guillain–Barré syndrome (GBS)

The possible risk of Guillain–Barré syndrome (GBS), an acute inflammatory demyelinating polyneuropathy, is a potential concern for large-scale vaccination programmes such as those against influenza or HPV [34,35]. A recent analysis of the VAERS database did not suggest an increased frequency of GBS onset following HPV4 vaccinations [36]. Indeed, considering the number of doses distributed from 1th June 2006 to 31th December 2008, the reporting rate (i.e. number of GBS case/dose distributed in the US) for GBS was 0.3 per 100,000 doses. This reporting rate should be compared with the background incidence of GBS in females aged 9–26 years, which was estimated to be of 1.57 cases per 100,000 subjects [36]. The proportional reporting ratio estimated does not meet the screening criteria for signal detection [36].

In a subsequent paper, Souayah et al. [37] estimated on the VAERS database that the weekly reporting rate of post quadrivalent vaccination within the first 6 weeks was 6.6 per 10,000,000. Such rate was higher than the one observed in general population [37], although this matter is still being discussed [38].

2.5. Systemic lupus erythematosus (SLE)

The incidence of HPV infection, as well as the risk of developing squamous intraepithelial lesions of the cervix, is higher in patients with SLE than in unaffected women [39]. Such increased risk may be related to the treatment for SLE or to other specific host-factors. The immunisation with the HPV vaccine has therefore a great importance in the prevention of cancer in these patients, as suggest by current guidelines [39].

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Gatto et al. recently reported on six patients, aged between 13 and 32 years, that developed SLE or a SLE-like disease after the first or the second dose of vaccine [40]. A second case series reported three similar situations following the vaccination against HPV [41]. Moreover, in a prospective open-label study with 26 SLE patients enrolled, 33% experienced a disease exacerbation after the vaccination [42]. By contrast, a case–control study failed to confirm these data as it did not show any significant difference in the number of exacerbations between vaccinated and non-vaccinated SLE patients [43]. The power of the study, however, was low and this may have prevented the detection of a small group of patients at higher risk [44].

In an analysis dating to the pre-HPV vaccine era, Siegrist et al. described the background incidence and the expected incidence of hospital admissions for several autoimmune conditions in the vaccine exposed groups [15]. In this work, the authors predicted a hospitalisation rate of two cases per 100,000 vaccine-exposed patients in a temporal association window of 6 weeks after immunisation [15]. These data suggest that a hospital admission for SLE may occur closely to the HPV vaccine shot without any causal relationship. We also recently reported about the absence of a significant increase in the number of hospital discharges for SLE in patients largely exposed to the vaccine [44]. All together, these reports indicate the lack of a significant correlation between HPV vaccination and SLE exacerbation.

2.6. Rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA)

Rheumatoid arthritis is a chronic inflammatory polyarthritis of unknown aetiology [45]. Unlike SLE, there is not a significant consensus on the increased risk for these patients to develop cervix lesion due to HPV infection. A recent study, however, showed the high prevalence of cervical HPV infection in Mexican women with RA [45]. Indeed the use of HPV vaccination in RA is widespread and at present information about the safety of HPV vaccine in patients with RA is scant, in particular on the possibility that the vaccine exacerbates the disease. Previous reports on other vaccines did not provide a significant relationship: few case series described the occurrence of transient rise of rheumatoid factor or some form of arthritis or RA [17,46,47]. These observations were, however, not confirmed by subsequent analyses showing the absence of increase of RA incidence in vaccinated subjects [17].

Interestingly we have more information on the safety of HPV vaccination and other forms of rheumatic disease. A recent cohort study reported by Heijstek et al. described the efficacy of the HPV vaccine in patients with Juvenile Idiopathic Arthritis (JIA) [48], the most common chronic rheumatic disease in childhood associated with increased susceptibility to infections due both treatments and disease effects [49]. In their prospective controlled observational study, Heijstek et al. included 68 JIA patients and 55 healthy girls aged 12–18 [48]. This study highlighted the safety and immunogenicity of the HPV vaccine and the absence of effect on JIA disease activity also in patients with high baseline disease activity or those using methotrexate [48].

2.7. Inflammatory bowel disease (IBD)

Patients with IBD represent a subgroup of subjects exposed to a high risk of cervical dysplasia due to HPV infection [50]. In a recent analysis, Badr Al-Baward et al. observed that the absence of a specific guideline for IBD patients represents a significant concern, mainly for women that were no longer receiving care from their paediatricians when the HPV vaccination became available [51].

The immunogenicity and the safety of HPV vaccine in patients with IBD have been assessed recently by Jacobson et al. in a small study with 37 IBD patients in treatment with immunosuppressive therapy [52]. The results of this analysis indicate that geometric mean titres for HPV-6, HPV-11, HPV-16 and HPV-18 did not qualitatively differ from healthy females and there were no clinically significant vaccine-associated adverse events [52].

2.8. Primary ovarian failure (POF)

A possible relationship between POF and HPV vaccine has been proposed in view of the temporal association of the occurrence of this condition and the vaccination [53,54]. Primary ovarian failure is a clinical condition with complex aetiology and 20–0% of the cases are characterised by an autoimmune mechanism [53]. The possible role of HPV vaccine as a trigger factor for an autoimmune insult against the ovary was hypothesised by Colafrancesco et al.; they described three young patients developing POF after HPV vaccination [53]. These cases, along with another previously described may raise concerns on the safety in specific patient at high risk due to unknown factors [53,54]. However, it is also possible that these cases were associated with a genetic risk factor as two of the three patients of Colafrancesco et al. were blood relative [53]. Analyses on a larger number of cases are required to determine conclusively on the association between POF and HPV vaccination.

2.9. Other autoimmune diseases

Several case reports and case series demonstrated the possible relationship between HPV vaccination and the occurrence or exacerbation of other, more rare autoimmune diseases [55–62]. In a recent paper, Cerami et al. reported on a case of acquired neuromyotonia following HPV vaccination [55]. It is unclear whatever the vaccination was responsible to trigger an immune-mediated disorder or only played a role in the acceleration of the onset of symptoms [55].

Another interesting report of an autoimmune disease following the inoculation of the HPV vaccine was reported by Della Corte et al., describing a case of type 2 autoimmune hepatitis that occurred to an 11 year old patient [57]. The patient had no previous history for liver, autoimmune diseases and did not report any recent medication other than the HPV vaccine [57]. As stated by the authors, the finding of autoimmune hepatitis in this patient may be coincidental and not related to the vaccine inoculation [57], although a report indicated the relationship between vaccination and the onset of autoimmune hepatitis in the case of the vaccine against hepatitis A [63].

Other cases of diseases described to occur closely in time to the HPV vaccine shot include linear IgA bullosus dermatitis [56], Henoch–Schonlein purpura [58], cutaneous vasculitis [58], Kikuchi–Fujimoto disease [59], erythema multiforme [61], acute cerebellar ataxia [60] and immune thrombocytopenic purpura [62]. Reports on these autoimmune diseases are however rare and it is difficult to draw any significant conclusion about their causal association with the HPV vaccination.

3. Discussion

Vaccine administration is usually safe and serious adverse events rare. Concerns about the safety of a newly introduced vaccine are commonly observed and are more likely to concern categories of patients that are rarely exposed to vaccines, as were adolescents before the introduction of the HPV vaccine [15].

One such case was the hypothesis of correlation between the Hepatitis B vaccine and MS in adolescents [64]. This hypothesis was supported by reports of temporal association between vaccine shot and MS onset [65,66] and were sufficient to fuel major vaccine-safety controversies. Despite two decades of studies did not find significant evidence of a correlation between this vaccine and MS onset, the confidence in the safety of the Hepatitis B vaccine was lost. Particularly as a result of this controversy, the hepatitis B immunisation programme in France largely failed and vaccine coverage remains below 25% [66].

These lessons about the effect of misinterpretation of the relationship between autoimmune disease and a vaccine should thus be considered when we discuss on the safety of a newly introduced vaccine.

The risk of misinterpretation of causal links is particularly high when we consider the association of autoimmune disease and the HPV

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vaccination, because the immunisation is recommended for groups of patients (young female) in which the incidence of autoimmune disease is high [15]. A confounding factor that adds to the problem is the lack of information on the established incidence of several diseases in some regions of the world; this aspect makes it difficult to assess the baseline incidence of a disease and its change after the introduction of a new vaccine.

Along with the risk of misinterpretation of a causal links, we should consider also the risk of ignoring and downplaying the relationship between a vaccine and an adverse event, especially in view of the presence of a well proven screening alternative [1,2,9]. In this view, women need to be informed on the relevance of Pap testing and that vaccines offer HPV infection prevention for a limited period and at some level of risk that is not fully determinable with the information available to date.

As the level of risk is not determinable fully at this time, the role of pharmacovigilance surveillance remains of paramount importance allowing the scientific community to detect unknown or rare events possibly related to the vaccine. The importance of such task increases considering possible adverse event that was not recognised during clinical studies, which are likely to be disregarded as vaccine-related by physician and parents.

An important aspect that may explain why in some but not all cases a causal relationship has been suggested is the possibility of a genetic predisposition to vaccine-induced autoimmune disease. This has been highlighted in a recent report of two blood relative patients [53]. No other studies have proposed a role of genetic factors in vaccine-induced autoimmune disease; however, genetic predisposition may justify why only a small number of subject who receive vaccination will subsequently develop them. The presence of genetic bases of adverse reactions has been described for several drugs and in some cases has reached the clinical practice. One of the most important examples is represented by the HLA-B*57:01 test for the Abacavir [67]. The introduction of this test resulted in a dramatic reduction of the cases of Abacavir hypersensitivity [67] and made the use of this drug significantly safer. Likewise, testing for HLA-B *1502 for carbamazepine in the Han Chinese population or HLA-A*3101 in subjects of Northern European ancestry [68] has been reported to be useful in reducing the risk of carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis. More recently HLA-B*13:01 has been associated with the development of the Dapsone hypersensitivity syndrome amongst patients with leprosy [69]. The identification of genetic bases for adverse events following vaccination should be actively investigated as it would provide a useful tool to prevent rare and serious diseases without impacting negatively on public confidence in immunisation programmes.

Abbreviations

ADEM	acute disseminated encephalomyelitis
NMO	neuromyelitis optica
MS	multiple sclerosis
SLE	systemic lupus erythematosus
POF	primary ovarian failure
JIA	Juvenile Idiopathic Arthritis

Take-home messages

- The human papilloma virus (HPV) vaccines are effective in women through 45 years of age for quadrivalent HPV vaccine and 55 years of age for bivalent HPV vaccine. Public health reimbursement covers the cost of vaccines for children up to 15 in most European countries and up to 26 in other Western countries.
- After the implementation of the HPV immunisation programme, several cases of autoimmune disease were reported to literature and safety surveillance programmes generating concerns about the safety of the vaccine.
- As autoimmune diseases occurs frequently in female adolescent, it is difficult to assess the role of HPV vaccine in the pathogenesis of these cases and no conclusive evidence has been reported thus far.
- Public confidence in the safety of a vaccine is of paramount importance and concerns in the absence of solid scientific evidence have already led to the failure of large immunisation programmes.
- Our study identifies the conditions in which HPV immunisation is most likely linked to the development of autoimmune diseases.
- The decision to vaccinate with HPV vaccine is a personal decision, not one that must be made for public health. HPV is not a lethal disease in 95% of the infections; and the other 5% are detectable and treatable in the precancerous stage.

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