As with all new vaccines, the Global Advisory Committee on Vaccine Safety has been reviewing the safety of HPV vaccines since they were first licensed in 2006. The World Health Organization (WHO) recommends the introduction of HPV vaccination into national immunization programmes where prevention of cervical cancer is a public health priority and the introduction is programmatically feasible [1]. While early detection of pre- and cancerous cells through screening programs has helped decrease incidence rates of cervical cancer in women aged 25-45 in the UK, for example [2], that decrease has plateaued in the past decade. While safety concerns about HPV vaccines have been raised, these have systematically been investigated: to date, the GACVS has not found any safety issue that would alter any of the current recommendations for the use of the vaccine.

The purpose of this update is to summarize the work of GACVS over the past six years in reviewing the safety of HPV vaccines. It is important to highlight and reiterate this work because a number of national immunization programs have been facing real and potential public losses of confidence in their programs as a result of increased negative publicity, even from safety issues that have been addressed.

To date, the GAVCS has reviewed evidence related to syncope, anaphylaxis, venous thromboembolism, adverse pregnancy outcomes, Guillain Barre Syndrome, and stroke [3]. It also examined concerns around the aluminium adjuvant used in HPV vaccines, with considerations around the toxicology of aluminium adjuvants and studies by investigators claiming that aluminium in the quantities used in vaccines are associated with adverse health outcomes [4]. Finally the Committee also reviewed the question of autoimmune disease, specifically around multiple sclerosis (MS), cerebral vasculitis, and an evolving concern over cases of complex regional pain syndrome (CRPS) and/or other chronic pain conditions following vaccination that have surfaced.

With respect to aluminium, the GACVS has had occasion to review the safety of the adjuvant on several occasions, beginning in 1999. At that time, deltoid muscle biopsies performed in France on a number of patients with a variety of complaints revealed in a small number the presence of a minute inflammatory focus of macrophages with associated necrosis. These localized lesions, called macrophagic myofasciitis (MMF), have been shown to contain aluminium salts [5, 6]. Since the location of the lesions in the deltoid muscle coincides with the usual site of injection for vaccines, these microscopic lesions may appear to be related to immunization. The investigators from the “Groupe d’études et de recherche sur les maladies musculaires acquises et dysimmunitaires” (GERMAAD) have suggested that vaccination and localized MMF lesions might be associated with a multi-system disorder. The GACVS has reviewed evidence regarding MMF on several occasions since that time and continues to reaffirm that, while MMF is clearly linked to a vaccination “tattoo” among some patients who have received an aluminium containing vaccine, the associated systemic symptoms related to that finding have never been scientifically proven. Statements about MMF were published in 1999, 2002 and 2004 [4]. While there have never been any published reports of MMF in recipients of HPV vaccines, there is no plausible reason to suspect that any reports of MMF would be associated with systemic symptoms following aluminium containing HPV vaccines any more than the finding of the histological lesion of MMF following hepatitis B vaccine and clinical symptoms.

In 2012, the GACVS reviewed two studies claiming an association between aluminium in vaccines and autism spectrum disorder [7, 8]. It found serious flaws in the two studies that limited their value even for hypothesis generation. In December 2013, the GACVS reviewed evidence related to HPV vaccine and
autoimmune disease, specifically multiple sclerosis [3]. While there remain case reports in the literature, multiple epidemiologic studies have not demonstrated any increased risk of autoimmune diseases, including MS, in studies, some of which have included girls who have received HPV vaccine compared to those who had not [9, 10, 11, 12].

Several papers have also been published pertaining to the finding of HPV L1 gene DNA fragments in clinical specimens following HPV vaccination [13, 14]. These papers claimed an association with clinical events of an inflammatory nature, including cerebral vasculitis. While the GACVS has not formally reviewed this work, both the finding of DNA fragments in the HPV vaccine and their postulated relationship to clinical symptoms, have been reviewed by panels of experts. First, the presence of HPV DNA fragments has been addressed by vaccine regulatory authorities who have clearly outlined it as an expected finding given the manufacturing process, and not a safety concern [15]. Second, the case reports [13] of adverse events hypothesized to represent a causal association between the HPV L1 gene DNA fragments and death were flawed in both clinical and laboratory methodology [16]. The paper described 2 fatal cases of sudden death in young women following HPV vaccine, one after 10 days and one after 6 months, with no autopsy findings to support death as result of cerebral vasculitis or an inflammatory syndrome. Thus the hypotheses raised in these papers are not supported by what is understood about the residual DNA fragments left over following vaccine production [17]: given the extremely small quantities of residual HPV DNA in the vaccine, and no evidence of inflammation on autopsy, ascribing a diagnosis of cerebral vasculitis and suggesting it may have caused death is unfounded.

In June 2013, the GACVS reviewed the concerns arising in Japan in regard to reports described as CRPS in a few cases, and other chronic pain conditions following HPV vaccine. At the time, GACVS found no evidence to suggest a causal link with the HPV vaccine, and recommended careful documentation of each case and definition of diagnostic criteria to guide management and causality assessment. The Committee has meanwhile continued to monitor the HPV vaccine and considered further issues during their meeting in December 2013 [3]. In Japan, an expert advisory committee has continued to meet and review the situation but has not yet reached a conclusion. It is acknowledged that the HPV vaccine may be a more painful injection, leading to frequent complaints of pain, which, in some settings, may trigger additional non-specific complaints [18, 19]. As to Complex Regional Pain Syndrome, this entity has been described following various forms of trauma, including injury, surgical procedures and injections. It is therefore plausible that CRPS could develop following the injection of any vaccine (however, such cases have been very rarely described in the literature [20]).

In summary, the GACVS continues to closely monitor the safety of HPV vaccines and, based on a careful examination of the available evidence, continues to affirm that its benefit-risk profile remains favorable. The Committee is concerned, however, by the claims of harm that are being raised on the basis of anecdotal observations and reports in the absence of biological or epidemiological substantiation. While the reporting of adverse events following immunization by the public and health care providers should be encouraged and remains the cornerstone of safety surveillance, their interpretation requires due diligence and great care. As stated before, allegations of harm from vaccination based on weak evidence can lead to real harm when, as a result, safe and effective vaccines cease to be used. To date, there is no scientific evidence that aluminium-containing vaccines cause harm, that the presence of aluminium at the injection site (the MMF “tattoo”) is related to any autoimmune syndrome, and that HPV DNA fragments are responsible for inflammation, cerebral vasculitis or other immune-mediated phenomena.
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HPV vaccine safety profile
Point of view of Public Health Authorities (Europe & Australia)

HPV vaccination in Europe, strengths and weaknesses

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Two vaccines against Human Papillomavirus (HPV) are available in the EU for cervical cancer prevention. Marketing authorization has been granted by the European commission to Gardasil in 2006 and to Cervarix in 2007. The European Medicine Agency (EMA) is responsible for the scientific evaluation of vaccines, as well as other human and veterinary drugs, including safety monitoring. The EMA is also responsible for maintaining EudraVigilance, a reporting system for side-effect reports. Through Eudravigilance, EMA manages signal-identification activities, rapid-alert, and responses to new safety signals in the EU. Safety records of both vaccines are very good, considering the evidence collected through both clinical trials and post-marketing surveillance. A recent study (a meta-analysis conducted selecting 7 different clinical trials, including about 44,000 women) showed that risk of serious adverse events was equal between vaccinated and not vaccinated women [1].

Introduction of HPV vaccination in the EU has been extremely quick, as compared to other newly licensed vaccines like pneumococcal, varicella or rotavirus. A total of 22 out of 31 EU/EEA countries have implemented a routine HPV vaccination programme [2]. Ten EU countries have also implemented catch-up programmes for a wider range of age groups (with the highest upper-limit of 40 years in Austria). In most cases the HPV vaccination programme is covered by the national health insurance system; in few cases vaccination is fully (Austria) or partially (Belgium and France) covered by the recipient.

However, reported vaccination coverage has been suboptimal in most of the EU countries. Only in UK and Portugal reported coverage in targeted age groups above 80%. The same applied to coverage for catch-up campaigns that ranged from 29% to 73% of the targeted population [2].

Lack of effective communication strategies might be the reason for the limited vaccine uptake in many EU countries. In fact, rumours of alleged serious adverse events after HPV vaccination has been strongly detrimental for the success of the vaccination programme in several EU countries. The EMA has been called several times during the last years to reply to rumours on HPV vaccine safety. Every time, EMA’s conclusion after careful assessment of the evidence, has been reassuring about the absence of correlation between HPV vaccination and alleged adverse events.

Events like sudden death, convulsions, autoimmune diseases (rheumatoid arthritis, multiple sclerosis, etc.) can happen to be coincidental with HPV vaccination, being those vaccines administered to adolescent or young women. Robust evidence has been collected so far to confirm the absence of causal link between HPV vaccination and such unfortunate events.

References


Experience with human papillomavirus vaccination (HPV) in Australia: the girls and women of France can be reassured that the vaccine is safe and the benefits are real

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Australia was the first country in the world to introduce a government funded national HPV vaccination program in April 2007, using a course of three doses of the quadrivalent HPV vaccine (‘Gardasil’). The program offered vaccination to all females aged 12 to 26 years until the end of 2009 and is now an ongoing program for both girls and boys, which is delivered in the first year of high school at age 12-13 years.

The program has delivered over 5.6 million doses of the vaccine to Australians so far, with a national vaccine register in place to monitor the uptake of the vaccine. Over 70% of school girls in Australia receive all three doses of the vaccine (1). The safety of the vaccine has been monitored in Australia throughout the program, with Australian reports confirming that the most common side effects of vaccination are local reactions at the site of injection and symptoms relating to the process of being vaccinated, such as headache and nausea.ainting has also been reported in Australia and rare cases of allergic reactions (anaphylaxis) – both of these conditions can occur with any vaccine and can be managed appropriately and safely by experienced vaccination teams/practitioners. Of direct relevance to the situation in France, cases of suspected multiple sclerosis that occurred among women who had been vaccinated were also investigated in Australia. Reassuringly an in-depth investigation found that there was no increase in the development of multiple sclerosis/demyelination disorders after HPV vaccination (2). In Australia, as in other countries, young women are in the age group at which serious illnesses such as multiple sclerosis can first develop. This means that reports such as these need to be thoroughly investigated but that if there is no increase in the rate at which the disease occurs among vaccinated women compared to those who are not vaccinated, then it does not support the vaccine causing the disease.

The Australian experience now forms part of the international experience with HPV vaccines which have been given to many millions of women and are demonstrably very safe and effective. Their safety has been confirmed in very large clinical trials prior to licensure, in surveillance data from multiple countries and in large scale studies which directly compare the health of vaccinated and unvaccinated women over time (3)(4). Parents and girls should feel reassured that these vaccines have been incredibly well studied and that all findings to date have shown that the vaccines are safe (5).

Australian data have shown that the HPV vaccine is already benefitting our population. We have recorded large falls in rates of infection with the HPV types the vaccine protects against (6), in genital warts (7) and in precancerous lesions of the cervix (8)(9).

It is truly a remarkable age in which to live, when we can protect our children against being infected with a cancer causing virus. We hope that the people of France will choose to support science over fear, knowing that the HPV vaccines have been well studied, indeed scrutinized, and found to be safe.

Dr Julia Brotherton  Prof Andrew Grulich

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