

**Statements by
WHO Global Advisory
Committee on Vaccine Safety
on the safety of human
papillomavirus (HPV) vaccines
2013–2016**



**World Health
Organization**

GACVS Safety update on HPV Vaccines

Geneva, 13 June 2013

At its meeting on 13 June 2013, GACVS reviewed updated information about the safety of HPV vaccines. The last review was conducted in June 2009. GACVS noted at the time that accumulating evidence on the safety of HPV vaccines was reassuring and that studies on HPV immunization had been initiated, along with capacity-building for adverse events monitoring. GACVS places a high priority on the ongoing collection of high-quality safety data in settings where the vaccine is being introduced.

In the past 4 years, safety data continued to accumulate as countries have initiated or expanded their immunization programs. The GAVI Alliance has also begun taking steps to make HPV vaccine available to women in developing countries where the burden of cervical cancer is considerable. To date, some 175 million doses of HPV vaccines have been distributed. A review of adverse events reported to the US Vaccine Adverse Event Reporting System following the distribution of over 23 million doses was published in 2009 (Slade 2009). Many countries where HPV is licensed now have considerable post-marketing data and no concerns have been identified. The manufacturers of currently available vaccines have developed pregnancy registries and are maintaining long term safety studies in conjunction with efficacy.

The Committee reviewed data from the United States, Australia, Japan and the manufacturers of Cervarix® (GlaxoSmithKline) and Gardasil® (Merck). Updates from the United States included an extension of the spontaneous reports to VAERS since the published review in 2009 as well as completed and planned studies from the Vaccine Safety Datalink. In Australia a new program targeting males started in February 2013 and data are just becoming available.

Data from all sources continue to be reassuring about the safety of the two vaccines. The data from VAERS now includes over 50 million doses distributed since 2006 and the profile has not changed significantly since the review in 2009. Reported adverse events not identified at the time of the first review, namely syncope and venous thromboembolism (VTE), were further investigated. For syncope, it continues to be reported but remains an event with a plausible relationship given the population and settings under which HPV vaccine is given. Adherence to a 15-minute observation period following vaccination has thus been strengthened as a recommendation. For VTE, while a rapid cycle analysis in the VSD did not find an increased risk, this is further being investigated with appropriate control for confounders such as oral contraceptive use, smoking and other risk factors in this population. Similarly, the VSD did not find any increased risk of Guillain-Barré syndrome or stroke.

In Australia, safety surveillance has been enhanced and the expert group continues to look at reported events. To date, with almost 7 million doses distributed, the previously investigated concern regarding an increased incidence of anaphylaxis was not confirmed. Following the extension of the vaccination program in males and enhanced surveillance since February 1 2013, preliminary results show the safety profile of Gardasil as similar to the profile among females.

The experience in Australia also provides useful lessons for countries introducing new vaccines in this age group, especially when vaccines are administered in a school based vaccination settings. In May 2007, soon after the introduction of the school-based program, 26 of 720 girls vaccinated at a girls' school developed symptoms including dizziness, palpitations, syncope or collapse, weakness, and aphasia. Four were transported by ambulance to hospital where further clinical evaluation found no organic basis for the reported symptoms. This cluster of adverse events was determined to be a result of a psychogenic response to vaccination. The event generated substantial media interest and public concern in Australia. (Buttery 2008, Gold 2010). Such cases require a prompt and thorough medical evaluation to establish a diagnosis and then an assessment of the relationship, if any, to the vaccine or vaccination as well as a proactive approach to communication, employing risk communication principles.

Surveillance from the two manufacturers found no signals that suggest a need for revisions to product labelling. Both have maintained surveillance of pregnancy outcomes following inadvertent vaccination during pregnancy. Detailed analyses of results have not found any new adverse outcomes related to HPV vaccination. For Gardasil, long term follow-up has now extended to over 8 years in the longest cohort, and no significant increase in newly diagnosed health events have been identified among those vaccinees. Updated analyses of the pregnancy registry have also been reassuring in that no adverse pregnancy outcomes have been observed beyond background expected rates. For Cervarix, the data have been similarly reassuring regarding pregnancy outcomes and specific events of interest such as immune mediated diseases. Risk of syncope and anaphylaxis have been added to the label to warn of these potential events, the former being also possibly related to conditions around the vaccination experience itself.

Finally, cases of complex regional pain syndrome (CPRS) were reported from Japan where over 8 million doses of HPV vaccines have been distributed. CPRS is a painful condition that emerges in a limb usually following trauma. Cases have been reported following injury or surgical procedures. It remains of unknown etiology and may occur in the absence of any documented injury. CPRS following HPV vaccines has received media attention in Japan with 5 reported cases most of which seem not compatible with typical CPRS cases. Review by an expert advisory committee could not ascertain a causal relationship to vaccination given lack of sufficient case information and in many cases could not reach a definitive diagnosis. While these are under investigation, Japan has continued to provide HPV vaccine in their national program.

In summary, 4 years after the last review of HPV vaccine safety and with more than 170 million doses distributed worldwide and more countries offering the vaccine through national immunization programs, the Committee continues to be reassured by the safety profile of the available products. Anaphylaxis and syncope, outcomes previously identified as concerns, have been addressed through further studies and appropriate revisions were made to the products labeling. Serious adverse events that have been reported as potential signals have been investigated in more detail, including Guillain-Barre Syndrome, seizures, stroke, venous thromboembolism, anaphylaxis, and other allergic reactions – many using rapid cycle analysis in the VSD in the United States. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries have not detected any adverse outcomes above expected rates.

The cases of chronic pain being reported from Japan deserve specific mention. To date there is little reason to suspect the HPV vaccine, given its growing use worldwide in the absence of a similar signal from elsewhere. Recognizing the public concerns voiced, the Committee urges careful documentation of each case and a thorough search for a definitive diagnosis by medical specialists in order to best guide treatment. A timely clinical assessment and diagnosis of each case followed by appropriate treatment is therefore essential.

Buttery JP, Madin S, Crawford NW, Elia S, La Vincente S, Hanieh S, Smith L, Bolam B. Mass psychogenic response to human papillomavirus vaccination. *Med J Australia* 2008;189(5):261-262

Gold MS, BATTERY J, McIntyre P. Human papillomavirus vaccine safety in Australia: experience to date and issues for surveillance. *Sexual Health* 2010;7:320-324

Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA*. 2009 Aug 19;302(7):750-7. doi: 10.1001/jama.2009.1201

GACVS Safety update on HPV Vaccines

Geneva, 17 December, 2013

At its meeting on 12 December 2013, GACVS reviewed evidence related to autoimmune disease and the HPV vaccine, with a focus on multiple sclerosis (MS). The last review was conducted in June 2013, where the Committee reviewed updated data from the United States, Australia, Japan and the manufacturers of Cervarix® (GlaxoSmithKline) and Gardasil® (Merck). With >175 million doses distributed worldwide and more countries offering the vaccine through national immunization programmes, the Committee continued to be reassured by the safety profile of the available products. Serious adverse events that have been reported as potential signals have been investigated in more detail and were not confirmed, including Guillain-Barré syndrome, seizures, stroke, venous thromboembolism, anaphylaxis and other allergic reactions. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries have not detected any adverse outcomes above expected rates.

While surveillance data and epidemiologic studies on HPV vaccine have continued to reassure, allegations have continued to surface in the media and elsewhere about the safety of the vaccine. Epidemiologic studies before and after licensure showed no increased risk of autoimmune disease, including MS. All along, such diseases have been under particularly careful investigation given their correspondingly high age-specific background incidence[1-3].

Examples of such studies include a register-based cohort study in Sweden and Finland that included almost 1 million girls aged 10-17 years, among whom close to 300,000 were vaccinated against HPV[4]. The study investigated whether vaccination was associated with an increased risk of autoimmune, neurological and thromboembolic events. The study results did not show evidence supporting associations between exposure to HPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events.

In the U.S., an observational study involving close to 200,000 girls and young women who had received at least one dose of HPV vaccine found no increased incidence of 16 investigated autoimmune diseases in the vaccinated compared to the non-vaccinated group[5]. The incidence of MS in the vaccinated cohort, for example, was not significantly higher than the non-vaccinated cohort (incidence rate ratio 1.37, 95% confidence interval 0.74 to 3.20). In a third study, a pooled analysis of data from 11 clinical trials involving nearly 30,000 participants over 10 years of age, of which 16,142 received at least one dose of Cervarix ® and 13,811 received either a placebo containing aluminum hydroxide or one of 2 different hepatitis A vaccines. No increased risk for the onset of autoimmune diseases after administration of Cervarix ® was observed in comparison to the control group[6].

The committee was provided with an overview of cases that were the subject of concern in France. These included one case of MS that had been adjudicated by a French Regional Commission for Conciliation and Compensation (CRCI). Another 14 cases of MS were reported through regional pharmacovigilance centres and/or the manufacturers to the European Medicines Agency. All 15 cases had been classified of “doubtful” causality, according to the French grading system[7].

In addition, the overview from France included results of a cohort study involving 2 million girls aged 12 to 16 showing a lack of increase in hospitalization rates for auto-immune diseases among those who received the HPV vaccine (2.1/10,000 patients/year) compared to those who did not (2.09/10,000 patients/year).

In summary, GACVS was presented with a series of cases of adverse events following the HPV vaccine. Multiple studies have demonstrated no increase in risk of autoimmune diseases, including MS, among girls who received HPV vaccine compared to those who had not. The Committee continues to be reassured by the safety profile of the vaccine, but notes the importance of continued surveillance and epidemiological investigation with an emphasis on the collection of high quality data; such data are essential for interpreting adverse events which occur following vaccination. Allegations of harm from vaccination based on incomplete information can lead to real harm when, as a result, effective vaccines are not used.

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March 12, 2014

**Global Advisory Committee on Vaccine Safety
Statement on the continued safety of HPV vaccination**

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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Global Advisory Committee on Vaccine safety

Statement on Safety of HPV vaccines

17 December 2015

Since first being licensed at the beginning of 2006, more than 200 million doses of HPV vaccines have been distributed globally. The World Health Organization (WHO) recommends that HPV vaccines be introduced into national immunization programmes provided that: prevention of cervical cancer and/or other HPV-related diseases constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered¹. The GACVS has systematically investigated safety concerns raised about HPV vaccines and has issued several reports in this regard². To date, it has not found any safety issue that would alter its recommendations for the use of the vaccine.

GACVS reviewed data from a recent retrospective cohort study from the French National Agency for Medicines and Health Products Safety on autoimmune conditions following HPV vaccination³. This large study of over 2 million girls showed a similar incidence in the vaccinated and unvaccinated populations for all conditions studied with the exception of Guillain-Barre syndrome where an increased risk was identified, mainly focused within 3 months after vaccination. This risk in the first few months after vaccination was very small (~1 per 100,000 vaccinated children) and has not been seen in other smaller studies. Additional studies in adequately sized populations will help evaluate this finding and, if confirmed, better

¹ See no. 43, 2014, PP. 465–492.

² See http://www.who.int/vaccine_safety/committee/topics/hpv/en/

³ Agence nationale de sécurité des médicaments et des produits de santé. Vaccins anti-HPV et risque de maladies autoimmunes : étude pharmacoépidémiologique.
http://ansm.sante.fr/content/download/80841/1023043/version/1/file/Ansm_Gardasil-Hpv2_Rapport_Septembre-2015.pdf

assess the magnitude of an eventual risk. This risk – small, if it exists at all – needs to be seen in the context of the long-lasting cancer-prevention benefits of HPV infection.

As well, concerns about complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) following HPV vaccination have been raised in certain geographic locations. These are both disorders of unclear and possibly heterogeneous etiology and the epidemiology of both conditions is not well characterized. CRPS is a chronic, painful condition usually affecting a single limb that typically follows an episode of trauma or immobilisation of a limb. The onset of symptoms of CRPS is difficult to define and is usually recognised among patients with continuing pain long after the trauma.

POTS is characterized by an abnormally large and sustained increase in heart rate when changing from a lying down to an upright position. This excessive heart rate increase is usually accompanied by a range of symptoms of orthostatic intolerance. Several clinical and epidemiological features contribute to POTS being especially challenging to study. Onset of POTS may be extremely difficult to ascertain retrospectively. POTS is probably relatively common in young adolescents, may be relatively infrequently diagnosed, and may be difficult to distinguish from the normal range of physiologic responses in this age group. Additionally, syncope is a common adverse event in response to immunization, especially among adolescents, which may lead to differential ascertainment of POTS in vaccinated and unvaccinated populations. In spite of the difficulties in diagnosing or fully characterizing these syndromes, review of pre- and post-licensure data provide no evidence that these syndromes are associated with HPV vaccination. Some symptoms of CRPS and POTS also overlap with symptoms of chronic fatigue syndrome (CFS) for which a published observational study reported no association with HPV vaccines⁴.

Although some cases of POTS reports were severe and long-lasting, the prognosis of POTS with symptomatic management is usually favourable, and symptoms in adolescents often resolve over time. Given the lack of specificity of some of the symptoms reported following HPV

⁴ Donegan K, Beau-Lejdstrom R, King B, et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine* 2013; 31:4961-7.

vaccination, clinicians are encouraged to refer severely-affected patients to physicians familiar with these syndromes for diagnosis and management. Prompt diagnosis and management by experienced clinicians may avoid harmful and unnecessary medical interventions and promote a prompt return to normal activities.

The circumstances in Japan, where the occurrence of chronic pain and other symptoms in some vaccine recipients has led to suspension of the proactive recommendation for routine use of vaccine in the national immunization program, warrants additional comment. Review of clinical data by the national expert committee led to a conclusion that symptoms were not related to the vaccine, but it has not been possible to reach consensus to resume HPV vaccination. As a result, young women are being left vulnerable to HPV-related cancers that otherwise could be prevented. As GACVS has noted previously, policy decisions based on weak evidence, leading to lack of use of safe and effective vaccines, can result in real harm⁵.

Continued pharmacovigilance will be important in order to ensure that concerns related to the use of HPV vaccines can be addressed with the best possible evidence. The impact of HPV vaccines on HPV-related clinical outcomes, including precancerous lesions is well established. The greatest health benefit globally is anticipated in countries without routine cervical cancer screening, where the vaccine is yet to be introduced. Enhanced spontaneous reporting of adverse events following immunisation should be put in place to ensure that those who could benefit the most from the intervention are vaccinated with adequate safety monitoring.

⁵ http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HP_V12_Mar_2014.pdf