Safety of HPV vaccines

Extract from report of GACVS meeting of 7-8 June 2017, published in the WHO Weekly Epidemiological Record of 14 July 2017

Since licensure in 2006, over 270 million doses of HPV vaccines have been distributed. GACVS first reviewed the safety data in 2007,[12] and subsequently in 2008,[13] 2009,[14] 2013,[15] 2014,[16] and 2015.[17] Early on, the Committee was presented signals related to anaphylaxis and syncope. The risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses, and syncope was established as a common anxiety or stress-related reaction to the injection. No other adverse reactions have been identified and GACVS considers HPV vaccines to be extremely safe.

Further safety data have been generated recently from Denmark, the United Kingdom and the United States of America and a comprehensive literature review has been conducted, prompting GACVS to review these new findings. Among the new data were studies looking at Guillain-Barré syndrome (GBS). The Committee has already assessed GBS as a signal and noted discrepant findings. Epidemiological studies assessing the risk of GBS following HPV vaccination have been published[18] including population cohort studies from Denmark and Sweden.[19] In 2017, in response to an online publication from France suggesting an increased risk,[20] a large self-controlled case-series study from the UK was conducted, based on a population where 10.4 million doses were administered. This most recent study found no significant increased risk for GBS after any dose of vaccine, in any of several risk periods assessed or for either vaccine brand.[21] In addition, GBS was specifically selected as an outcome in studies from the US using the Vaccine Adverse Events Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). GACVS was presented with new data from VAERS following 60 million distributed doses, and the VSD data with over 2.7 million doses administered until the end of 2015. No association between HPV vaccine and GBS was identified. Both the UK and US studies concluded, based on their respective data, that a risk of >1 case of GBS per million doses of vaccine could now be excluded.

In addition, GACVS was presented with new studies assessing other safety concerns, again from the US, as well as from Denmark. These studies included examination of specific outcomes that included complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency, primary ovarian failure, and a further look at the risk of venous thromboembolism. With now large population level data from several countries, the Committee saw no new evidence for a causal association between HPV vaccine and those conditions. While safety data from Denmark and Sweden for >3 million women aged 18–44 years showed an apparent increased risk for celiac disease, the investigators considered that, most likely, this represented an unmasking of an existing condition during the vaccination visit rather than a causal association. Overall the study did not raise any other autoimmune safety issues of concern.

As HPV vaccine is often administered during potential childbearing years it is important to establish the safety profile in pregnant women when inadvertent administration occurs. To date no safety concerns have arisen during the pre-licensure clinical trials or in post-licensure surveillance.[22] These reassuring data now include a recent national cohort study from Denmark that assessed 540 805 pregnancies.[23] In addition, new data from the VSD for >92 000 eligible pregnancies were presented to the Committee. No adverse obstetric, birth or structural abnormality outcomes were observed. Inadvertent administration of HPV vaccine during pregnancy has no known adverse outcomes in either mother or infant.

CRPS and POTS continue to be presented as case reports in association with HPV vaccination, particularly from Denmark and Japan. These were initially assessed by GACVS in 2015.[24] These conditions include a spectrum of diverse symptoms, making assessment using administrative health collections challenging. In June 2017, new data from Japan that assessed cases with diverse symptoms, including pain and motor dysfunction, were presented to the Committee. The cases were identified from a nationwide epidemiological survey involving multiple hospital medical departments of various disciplines including pain, neurology, rheumatology, paediatrics and psychiatry/psychosomatic medicine. These complex syndromes manifested in both sexes, although were more common in girls, and occurred in both vaccinated and unvaccinated individuals. The Committee concluded that since their last review, there is still no evidence to suggest a causal association between HPV vaccine and CRPS, POTS or the diverse symptoms that include pain and motor dysfunction.

Also in 2017, the WHO commissioned a systematic review of serious adverse events (SAEs) following HPV vaccines. A draft was presented to GACVS at the meeting. Using the GRADE system to systematically assess the quality of evidence, the quality of evidence in the studies was considered high across randomized controlled trials. The outcomes considered were all

SAEs, medically significant conditions, new onset of chronic diseases, and deaths. Data for 73 697 individuals were reviewed. Lower level studies were excluded in favour of the large body of higher level evidence available. For all outcomes, the evidence from randomized controlled trials was supported by good quality cohort studies, with no difference in rates of selected SAEs between exposed and unexposed to HPV vaccine observed.

There are now accumulated safety studies that include several million persons[25] and which compare the risks for a wide range of health outcomes in vaccinated and unvaccinated subjects. However, despite the extensive safety data available for this vaccine, attention has continued to focus on spurious case reports and unsubstantiated allegations. The Committee continues to express concern that the ongoing unsubstantiated allegations have a demonstrable negative impact on vaccine coverage in a growing number of countries, and that this will result in real harm.[26] While ongoing monitoring and collection of robust data are important to maintain confidence, one of the challenges associated with the continued generation of data is that artefacts will be observed, which could pose further challenges for communication when taken in haste, out of context, and in the absence of the overall body of evidence.

GACVS discussed the importance of ensuring that immunization policy-makers and other stakeholders have ready access to articulate summaries of the vaccine safety information, to assist in evidence-based decision-making. One concrete step will be to update the HPV adverse reaction rate sheet, to reflect the most recent evidence available.[27]

Where HPV vaccination programmes have been implemented effectively, the benefits are already very apparent. Several countries that have introduced HPV vaccines to their immunization programme have reported a 50% decrease in the incidence rate of uterine cervix precancerous lesions among younger women. In contrast, the mortality rate from cervical cancer in Japan, where HPV vaccination is not proactively recommended, increased by 3.4% from 1995 to 2005 and is expected to increase by 5.9% from 2005 to 2015. This acceleration in disease burden is particularly evident among women aged 15–44 years.[28] Ten years after introduction, global HPV vaccine uptake remains slow, and the countries that are most at risk for cervical cancer are those least likely to have introduced the vaccine. Since licensure of HPV vaccines, GACVS has found no new adverse events of concern based on many very large, high quality studies. The new data presented at this meeting have strengthened this position.

---

[12] See No. 28/29, 2007, pp. 245–260.

[13] See No. 5, 2009, pp. 37–40.

[14] See No. 32, 2009, pp. 325–332.

[15] See No. 29, 2013, pp. 301–312.

[16] See No. 7, 2014, pp. 53–60.

[17] See No. 3, 2016, pp. 21–32.

[18] Grimaldi-Bensouda L, Rossignol M, Koné-Paut I et al. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. Journal of Autoimmunity. 2017;79:84–90.

[19] Arnheim-Dahlström L, Pasternak B, Svanström H et al. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. Bmj. 2013;347:f5906.

[20] Agence nationale de sécurité du médicament et des produits de santé. Vaccins anti- HPV et risque de maladies auto-immunes: étude pharmaco-épidémiologique, 2015. Available only in French language at http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Vaccination-contre-les-infections-a-HPV-et-risque-de-maladies-auto-immunes-une-etude-Cnamts-ANSM-rassurante-Point-d-information, accessed June 2017.

[21] Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. Vaccine. 2017;35(13):1729–1732.

[22] Bonde U, Joergensen JS, Lamont RF, et al. Is HPV vaccination in pregnancy safe? Human vaccines & immunotherapeutics. 2016;12(8):1960–1964.

[23] Scheller NM, Pasternak B, Mølgaard-Nielsen D et al. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. New England Journal of Medicine. 2017;376(13):1223–1233.

[24] See http://www.who.int/vaccine_safety/committee/reports/Dec_2015/en/

[25] Gee J, Weinbaum C, Sukumaran L et al. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. Human vaccines & immunotherapeutics. 2016;12(6):1406–1417.

[26] See http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12_Mar_2014.p

[27] See http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/

[28] Iwata S et al. Consensus statement from 17 relevant Japanese academic societies on the promotion of the human papillomavirus vaccine. Vaccine. 2017;35:2291–2292.

Full report of GACVS meeting of 7-8 June 2017, published in the WHO Weekly Epidemiological Record of 14 July 2017

Extract from report of GACVS meeting of 2-3 December 2015, published in the WHO Weekly Epidemiological Record of 22 January 2016

Since first being licensed at the beginning of 2006, >200 million doses of HPV vaccines have been distributed globally. WHO recommends that HPV vaccines be introduced into national immunization programmes provided that: prevention of cervical cancer and/or other HPV-related diseases constitute 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 considered.[4] The GACVS has systematically investigated safety concerns raised about HPV vaccines and has issued several reports in this regard.[5] To date, GACVS 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 vaccination.[6] This large study of >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 assess the magnitude of an eventual risk. This risk, which is small, if it exists at all, needs to be seen in the context of the long-lasting cancer-prevention benefits of HPV infection.

In addition, 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 immobilization 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 vaccination, especially among adolescents, which may lead to differential ascertainment of POTS in vaccinated and unvaccinated populations.

Despite the difficulties in diagnosing or fully characterizing CRPS and POTS, reviews 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 for which a published observational study reported no association with HPV vaccines.[7]

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 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 HPV vaccine in the national immunization programme, 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 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 harm.[8]

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 immunization should be put in place to ensure that those who could benefit the most from the intervention are vaccinated with adequate safety monitoring.

---

[4] See No. 43, 2014, pp. 465–492.

[5] See http://www.who.int/vaccine_safety/committee/topics/hpv/en/

[6] Agence nationale de sécurité des medicaments 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

[7] 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; 31:4961–4967.

[8] See http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12_Mar_2014.p

Full report of GACVS meeting of 2-3 December 2015, published in the WHO Weekly Epidemiological Record of 22 January 2016

Extract from report of GACVS meeting of 11-12 December 2013, published in the WHO Weekly Epidemiological Record on 14 February 2014

GACVS reviewed evidence related to autoimmune disease and the HPV, with a focus on multiple sclerosis (MS). The last review was conducted in June 2013, when the Committee reviewed updated data from the USA, 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 has not detected any adverse outcomes above expected rates.

While surveillance data and epidemiologic studies on HPV vaccine have remained reassuring, 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. Since the introduction of HPV vaccines, such diseases have been under particularly careful investigation given their correspondingly high age-specific background incidence.9, 10, 11

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 almost 300 000 were vaccinated against HPV.12 The study investigated whether vaccination was associated with an increased risk of autoimmune, neurological or thromboembolic events. The study results did not show evidence of any association between exposure to HPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events.

In the USA, an observational study involving almost 200 000 girls and young women who had received at least 1 dose of HPV vaccine found no increased incidence of 16 investigated autoimmune diseases in the vaccinated compared to the non-vaccinated group.13 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 0.74–3.20). In a third study, a pooled analysis of data from 11 clinical trials involving nearly 30 000 participants aged >10 years, of which 16 142 received at least 1 dose of Cervarix and 13 811 received either a placebo containing aluminium hydroxide or 1 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.14

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. 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 as being of "doubtful" causality, according to the French grading system. In addition, the overview from France included results of a cohort study involving 2 million girls aged 12–16 showing a lack of increase in hospitalization rates for autoimmune 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 administration of the HPV vaccine. Multiple studies have demonstrated no increase in risk of autoimmune diseases, including MS, among girls who have received HPV vaccine compared to those who have not. The Committee remains reassured by the safety profile of the vaccine, but noted the importance of continued surveillance and epidemiological investigation with an emphasis on the collection of high quality data; such data are essential for interpretation of any adverse events which may occur following vaccination. Allegations of harm due to vaccination based on incomplete information may lead to unnecessary harm when effective vaccines are not used.

---

[9] Siegrist CA. Autoimmune diseases after adolescent or adult immunization: what should we expect? CMAJ. 2007 Nov 20;177(11):1352-4.

[10] Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J. 2007 Nov;26(11):979-84.

[11] Callréus T, et al. Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events. Vaccine. 2009 May 14;27(22):2954-8.

[12] Arnheim-Dahlström L, et al. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ. 2013 Oct 9; 347.

[13] Chao C et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med. 2012 Feb;271(2):193-203.

[14] Descamps D, et al. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. Hum Vaccin. 2009 May;5(5):332-40.

Full report of GACVS meeting of 11-12 December 2013, published in the WHO Weekly Epidemiological Record on 14 February 2014