World Health Organization

Global Vaccine Safety

Safety update 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.

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[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.pdf

[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.

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