World Health Organization

Global Vaccine safety
Essential Medicines & Health Products
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INFORMATION SHEET

OBSERVED RATE OF VACCINE REACTIONS

HUMAN PAPILLOMA VIRUS VACCINE

December 2017

Types of vaccines

Currently available HPV vaccines consist of recombinant viral vaccine proteins containing highly purified virus-like particles (VLP) which are the protein shells of the HPV virus (major capsid protein L1). The VLP contain no viral DNA. Thus, they cannot infect cells, reproduce or cause disease. The VLP for each virus genotype are purified and then adsorbed onto an adjuvant. The available vaccines differ in the number of HPV genotypes that they contain, the way that they are manufactured and the adjuvant that they contain. Both 2v-HPV and 4v-HPV vaccines are highly immunogenic and prevent primary infection with the HPV genotypes and prevent CIN 2/3 adenocarcinoma. Pre-licensure trials indicate a broadly similar safety profile for minor and severe adverse events for each of the vaccines. (See table 1)

Table 1

Name	Vaccine antigens	Excipients
Gardasil 4v	4v-HPV VLP from genotypes 6, 11, 16, 18	Produced in recombinant *S. cerevisiea* culture. Aluminum hydroxyphosphate, Polysorbate 80, sodium borate and L Histidine
Gardasil 9v	9v-HPV VLP from genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58	Produced using recombinant Saccharomyces cerevisiae. Aluminium (provided as AAHS), sodium chloride, L-histidine, polysorbate 80, sodium Borate and yeast protein. Does not contain preservative or antibiotics.
Cervarix 2v	2v-HPV VLP from genotypes 16, 18	Produced in recombinant Baculovirus expression vector system. Aluminum hydroxide plus deacylated onophosphoryl l ipid A used as an adjuvant (AS04)

Safety summary and information sheet

As at June 2017 it is estimated that over 270 million doses of the HPV vaccine have been distributed. Post-licensure surveillance data concerning the safety profiles for each of the HPV vaccine brands have detected no serious safety issues to date except rare reports of anaphylaxis. The safety of the HPV vaccine has been regularly reviewed by the Global Advisory Committee for Vaccine Safety (GACVS) who have not identified any safety concerns http://www.who.int/vaccine_safety/committee/topics/hpv/en/

This HPV information sheet was adapted from the earlier version first published in June 2012 following a systematic literature review, conducted in December 2016, which included available evidence on the serious adverse events associated with HPV vaccines.

A large body of randomised controlled trial evidence comprising 72,835 subjects provided data upon which the rates of serious adverse events were calculated. In addition, several large cohort studies provided evidence for specific health outcomes, predominantly autoimmune diseases. The specific methodology, articles' profiles and quality of evidence that compromise the systematic review can be accessed through http://www.who.int/vaccine_safety/HPV_vaccination_safety_report_AHTA_dec17.pdf

Adverse events

Minor adverse events (See table 2)

Local adverse events

The 9v-HPV vaccine was well-tolerated, and most adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity. The safety profiles were similar in 4v-HPV and 9v-HPV vaccinees. Among females aged 9 through 26 years, 9vHPV recipients had more injection-site adverse events, including swelling (40.3% in the 9vHPV group compared with 29.1% in the 4v-HPV group) and erythema (34.0% in the 9vHPV group compared with 25.8% in the 4v-HPV group). Males had fewer injection site adverse events. In males aged 9 through 15 years, injection site swelling and erythema in 9vHPV recipients occurred in 26.9% and 24.9%, respectively. Rates of injection-site swelling and erythema both increased following each successive dose of 9vHPV. (See table 2) https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a3.htm

Systemic adverse events

In clinical trials prior to licensure of the 4v-HPV vaccine, systemic adverse events were monitored for the first 15 days post vaccination. The only adverse event reported that occurred in greater than 1% of vaccines and occurred more frequently than placebo was pyrexia (10.1 versus 8.4% according to EMEA CHMP (2006), respectively).

A number of other systemic adverse events, of minor nature were reported, but these occurred with less than a 0.5% difference in the vaccinated group. Mild systemic adverse events possibly related to vaccination included headache, dizziness, myalgia, arthralgia, and gastrointestinal symptoms (nausea, vomiting abdominal pain). In a direct comparison of the 2v-HPV and 4v-HPV vaccines, systemic reactions were reported at comparable rates, with the exception of fatigue [49.8% (95% CI: 45.5-54.2) vs. 39.8% (35.6-44.1)] and myalgia [27.6% (95% CI: 23.8-31.6) vs. 19.6% (16.3-23.3)], which were reported more frequently amongst recipients of the 2v-HPV vaccine. (See table 2)

Severe or serious adverse events – systematic review (See table 3)

This comprehensive systematic review containing a large body of high-level evidence is very consistent in finding no evidence of severe or serious adverse events associated with difference in the rate of Serious Adverse Events (SAE) between people who have received either the 2v-HPV or 4v-HPVvaccines and people who received a placebo or a control vaccine. Good quality cohort studies of specific autoimmune and other SAEs also found no relationship between exposure to HPV vaccination and development of these outcomes.

The results of the analysis for the specific outcomes are summarised in the Summary of Findings Table using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology http://www.gradeworkinggroup.org/.

These outcomes included SAE, new onset chronic disease and medically significant conditions. A comparison of effects show that there is no absolute event rate difference for any of these conditions in those vaccinated with HPV vaccine (2v-HPV or 4v-HPV) and placebo (or those vaccinated with a control vaccine). For auto-immune disease, venous thromboembolism, multiple sclerosis and other demyelinating conditions safety data is available from high quality cohort studies which have not demonstrated differences in the rates of these conditions in those exposed or unexposed to the HPV vaccine. Rare or very rare adverse events (such as auto-immunity) can only be evaluated for safety using post-licensure surveillance studies because randomised controlled trials do not have adequate power to detect such events.

The current estimated rate of anaphylaxis is 1.7 cases per million doses. This is consistent with the rate of anaphylaxis following other vaccines. The rates for anaphylaxis for other vaccines given to children and adolescents range from 0 to 3.5 per million doses in international studies which have used different case definitions for anaphylaxis.

Other vaccine safety issues

Postural Orthostatic Tachycardia Syndrome (POTS), Chronic Regional Pain Syndrome (CRPS), Chronic Fatigue Syndrome (CFS). POTS, CRPS, and CFS are reported as adverse events following HPV immunization. These conditions most commonly occur independent of immunisation and their pathogenesis is poorly understood. Their causal association with immunization is not established. However, it is plausible that CRPS may occur in a limb that has been the site of an injected vaccine as other causes of local trauma may trigger this condition. CRPS has been described, in case reports, to present soon after immunisation. The association between POTS and CRPS has been reviewed by the European Medicines Agency (EMA) who have concluded that there is no causal association between these conditions and HPV immunization.

Death Deaths were reported in nearly every study, and the number of deaths was very low. No death was considered vaccine related in the Gardasil studies, and two of the Cervarix studies reported the causes of death without commenting their causality.

HPV vaccine in combination with other vaccines. Assessment of concomitant use of the 4v-HPV vaccine and recombinant Hepatitis B vaccine showed no increase in adverse events. Concomitant use of the 2v-HPV vaccine with combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine to girls and young women was generally well tolerated.

HPV vaccine in pregnancy. In the absence of well-controlled studies in pregnant women, vaccination with HPV vaccine is not recommended in pregnancy as a precautionary measure. However, some data is available because pregnant women have been enrolled in phase III clinical trials with known pregnancy outcomes and through the establishment of pregnancy registers. In a combined analysis of pregnancy outcomes for women aged up to 45 years, the administration of 4v-HPV human papillomavirus vaccine to women who became pregnant during the phase III clinical

trials did not appear to negatively affect pregnancy outcomes. A pooled analysis of two randomized controlled trials on the risk of miscarriage with 2v-HPV vaccine provided no evidence overall for an association between HPV vaccination and risk of miscarriage. Of 517 reports of pregnancies enrolled on a register, rates of spontaneous abortions and major birth defects were not greater than those in the unexposed population. An analysis of phase III trials and post-marketing data identifying reports of 90 pregnancies within 30 days of vaccination showed no increased risk of spontaneous abortion, fetal malformations, or adverse pregnancy outcomes in the general population.

Syncope in adolescent girls. Post-marketing surveillance has documented a number of cases of syncope in adolescent girls. Possibly the rate of syncope is higher when the HPV vaccine is delivered as part of a school programme and vaccine providers should have measures in place to prevent syncope and syncope-related injury from occurring.

The WHO vaccine reaction rates information sheets

WHO vaccine reaction rates information sheets are primarily designed for use by national public health officials and immunization programme managers but this information may interest others. These sheets can be used for causality assessment of Adverse Events Following Immunization (AEFI) because they describe vaccine product related reactions. Also this information may help in preparing communication materials. WHO has developed these rate sheets through a systematic process involving global vaccine safety and vaccine experts.

For the reviews of serious adverse events, academics who specialize in systematic literature reviews and assessment of evidence quality using the GRADE process have been contracted. This material is then reviewed by GACVS (or a GACVS subcommittee) and also by the WHO Immunization, Vaccines and Biologicals division. GACVS approves the material before review by the WHO Assistant Director General's office.

Publications of the WHO vaccine reaction rates information sheets can be found at http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/. Information sheets are periodically reviewed on a need based manner with newer vaccines being more frequently reviewed and updated than those established for many decades.

Details of minor and severe adverse reactions following immunization including the expected rates of vaccine reactions have been included when these are available in the published literature. Since published literature often does not distinguish between severe and serious AEFI, the terminologies used in this rate sheet have not considered them separately.

Table 2
Summary of minor adverse events – local and systemic

Outcome	Description	Rate per 100 doses		
		9v-HPV	4v-HPV	2v-HPV
Local	Injection site reaction		83	----
	Pain		-----	78
	Swelling	26.9 - 40.3	25	26
	Erythema	24.9 - 34.0	-----	30
	Severe - injection site erythema and/or swelling > 2 inches in size and pain severe		5.7	-----
Systemic	Fatigue		----	33
	Pyrexia		13	3
	Urticaria		3	28
	Headache		26	30
	Myalgia		2	28
	Arthalgia		1	10
	Gastrointestinal disorders		17	13
	Rash		----	1
	Urticaria		------	0.46 100

Table 3

GRADE Summary of Findings Table (grading of quality of scientific evidence) for severe adverse events following HPV vaccines*

Participants: Males and females of any age

Settings: Worldwide

Comparison: Gardasil or Cervarix vs placebo or control vaccine

Outcome	Data size and source	Comparison of effects*		Size of effect	Certainty of the evidence (GRADE)
		Vaccine	Control		
Serious adverse events (1 month – 9yrs follow-up)	**Gardasil versus placebo**: Based on data from 28,671 subjects in 7 randomised controlled trials	858.2 / 100,000	935.8 / 100,000	No Difference	⊕⊕⊕⊕ HIGH
		Absolute event rate difference: Rate per 100,000 (%, 95%CI) -77.6 **(0.08%, 95%CI -0.2%, 0.3%)** Relative difference: RR 0.93 (95% CI 0.17.22,1)			
	Gardasil versus control vaccine: Based on data from 3,810 subjects in 1 randomised controlled trial	733.8 / 100,000	841.2 / 100,000	No Difference	⊕⊕⊕⊕ HIGH
		Absolute event rate difference: Rate per 100,000 (%, 95%CI) -107.4 **(0.11%, 95%CI -0.5%, 0.7%)** Relative difference: RR 0.87 (95% CI 0.43, 1.78)			
	Cervarix versus placebo: Based on data from 14,268 subjects in 10 randomised controlled trials	1836.6 / 100,000	1876.2 / 100,000	No Difference	⊕⊕⊕⊕ HIGH
		Absolute event rate difference: Rate per 100,000 (%, 95%CI) -39.6 **(0.04%, 95%CI -0.4%, 0.5%)** Relative difference: RR 0.91 (95% CI 0.68, 1.22)			
	Cervarix versus control: Based on data from 30,843 subjects in 8 randomised controlled trials	11,676.8/ 100,000	11,595.7 / 100,000	No Difference	⊕⊕⊕⊕ HIGH
		Absolute event rate difference: Rate per 100,000 (%, 95%CI) 81.1 **(0.1%, 95%CI -0.8%, 1.0%)** Relative difference: RR 1.01 (95% CI 0.95, 1.07)			
New onset chronic disease (1 month – 9 yrs)	**Cervarix versus placebo:** Based on data from 9,511 subjects in 9 randomised controlled trials	1240.1 / 100,000	1306.6 / 100,000	No Difference	⊕⊕⊕⊕ HIGH
		Absolute event rate difference: Rate per 100,000 (%, 95%CI) -66.5 **(0.07%, 95%CI -0.4%, 0.5%)** Relative difference: RR 0.83 (95% CI 0.58, 1.20)			
	Cervarix versus control: Based on data from 30,349 subject in 7 randomised controlled trials	4680.8 / 100,000	5079.9 / 100,000	No Difference	⊕⊕⊕⊕ HIGH
		Absolute event rate difference: Rate per 100,000 (%, 95%CI) -399.1 **(0.4%, 95%CI -0.9%, 0.9%)** Relative difference: RR 0.93 (95% CI 0.84, 1.03)			

Outcome	Data size and source	Comparison of effects*		Size of effect	Certainty of the evidence (GRADE)
		Vaccine	Control		
Medically significant conditions (1 month – 9 yrs)	**Cervarix versus placebo:** Based on data from 7,623 subjects in 6 RCTs	8201.4 / 100,000	6949.6 / 100,000	No Difference	⊕⊕⊕⊕ HIGH
		Absolute event rate difference: Rate per 100,000 (%, 95%CI) 1251.8 **(1.25%, 95%CI 0.04%, 2.5%)** Relative difference: RR 1.15 (95% CI 0.88, 1.50)			
	Cervarix versus control: Based on data from 28,498 subjects in 4 RCTs	29,372.9 / 100,000	30,069.4 / 100,000	No Difference	⊕⊕⊕⊕ HIGH
		Absolute event rate difference: Rate per 100,000 (%, 95%CI) -696.5 **(0.7%, 95%CI -0.4%, 1.8%)** Relative difference: RR 0.98 (95% CI 0.92, 1.05)			
Auto-immune diseases following HPV vacci-nation	Data from 4 high quality cohort studies	No difference in rates of most autoimmune diseases between those exposed to vaccine and those unexposed. No findings equated to a safety signal.		No Difference	⊕⊕⊕2 MODERATE
Venous Thrombo-embolism	Data from 2 high quality cohort studies	No difference in the rate of thromboembolism in those exposed to vaccine and those unexposed.		No difference	⊕⊕⊕2 MODERATE
Multiple sclerosis and other demyeli-nating conditions	Data from 1 high quality cohort study	Exposed MS	Unexposed	No Difference	⊕⊕⊕2 MODERATE
		6.12 / 100,000 person years	21.54 / 100,000 person years		
		IRR 0.90 (95%CI 0.70, 1.15)			
		Other: 7.54 / 100,000 person years	16.14 / 100,000 person years		
		IRR 1.00 (95%CI 0.80, 1.26)			

*Systematic review of serious adverse events associated with HPV vaccination - http://www.who.int/vaccine_safety/HPV_vaccination_safety_report_AHTA_dec17.pdf

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