World Health Organization
Global Vaccine Safety,
Immunization, Vaccines and Biologicals
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
HUMAN PAPILLOMA VIRUS VACCINE

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The Vaccines

Currently available HPV vaccines are a recombinant viral protein vaccine containing highly purified virus-like particles (VLP) which are the protein shells of the HPV virus (major capsid protein L1) formed by recombinant DNA techniques. 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 Bivalent and Quadrivalent 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 serious adverse events for each of the vaccines. Post-licensure surveillance data concerning the safety profiles for each vaccine have detected no safety issues to date (as at November 2011) except rare reports of anaphylaxis.

Types of vaccines

	Vaccine antigens	Excipients
Quadrivalent	VLP from genotypes 6, 11, 16, 18	Produced in recombinant *S. Cerevisiea* culture. Aluminum hydroxyphosphate, Polysorbate 80, sodium borate and L Histidine
Bivalent	VLP from genotypes 16, 18	Produced in recombinant Baculovirus expression vector system. Aluminum hydroxide plus deacylated monophosphoryl Lipid A used as an adjuvant (AS04)

Adverse events

Mild adverse events

Local adverse events

Injection site pain is very common, having been reported in up to 80% of vaccinees for Bivalent (EMEA CHMP, 2007) and Quadrivalent vaccine (Markowitz et al., 2007). Severe pains (spontaneous pain or pain that prevented normal activity) was reported for approximately 6% (EMEA CHMP, 2007) of vaccinees. In pre-licensure placebo controlled clinical trials using the Quadrivalent vaccine, injection site reactions consisted of pain (84%) erythema (up to 25%) and swelling (25%), with pain occurring more commonly than in the placebo groups - both for saline only placebo (pain - 49%) and aluminium placebo (pain-75%). Local adverse reactions following Bivalent HPV vaccine were similar with 78% of vaccine recipients experiencing injection site pain compared with 52% who received the adjuvant alone or 59% who received Hepatitis A vaccine. In a trial comparing the two HPV vaccines in over 1,000 women aged 18 to 45, local reactions occurred more frequently with Bivalent than Quadrivalent vaccine. Injection site reactions included pain (92.9% Bivalent, 71.6% Quadrivalent), redness (44.3% Bivalent, 25.6% Quadrivalent) and swelling (36.5% Bivalent, 21.8% Quadrivalent) (Einstein et al, 2009).

Systemic adverse events

In clinical trials prior to licensure of the Quadrivalent 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 an occurrence 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 Bivalent and Quadrivalent 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 Bivalent vaccine (Einstein et al., 2009).

Severe adverse events

In pre-licensure trials, no severe adverse events attributable to the vaccine were recorded for either the Quadrivalent or Bivalent vaccine. Post-licensure clinical trials have included a randomized comparative cohort study on the safety of the Quadrivalent and Bivalent vaccines in 18-45 year old women. Systemic adverse events were monitored for 7 days and 30 days post vaccination. No clinically relevant differences were seen between the vaccinated groups (Quadrivalent vs Bivalent) with regard to new onset chronic disease which also included new onset autoimmune disease (Einstein MH et al., 2009). Follow-up of this cohort 18 months after the last dose of HPV vaccine (at 24 months) were similar between groups (Einstein MH et al., 2011).

HPV vaccine and post-marketing surveillance. As of September 15, 2011, approximately 40 million doses of Quadrivalent vaccine were distributed in the U.S. and VAERS received a total of 20,096 reports of adverse events following Quadrivalent vaccination: 19,075 reports among females and 569 reports for males, of which 504 reports were received after the vaccine was licensed for males in October 2009. Of the total number of reports, 92% were considered to be non-serious, and 8% were considered serious (VAERS 2011). Analysis of the currently available reports has not shown an excessive number of serious or unexpected adverse events (Slade et al., 2009). In particular, further investigation of case reports of Guillain-Barré syndrome, blood clots, and deaths have not revealed any pattern suggesting a causal association with vaccination. Analysis of conditions of interest arising among vaccinated and unvaccinated women using the Vaccine Safety Data link was generally reassuring. A non-significant excess of deep vein thrombosis was observed among women who had other risk factors. One vaccine-associated case of anaphylaxis was observed, with an overall rate of one per 1.7 million doses (95% CI 0.04, 9.3) (Gee et al., 2011).

In Australia, over 6 million doses of Quadrivalent vaccine have been used (as of June 2010) with 1534 adverse events reported (Therapeutic Goods Administration, 2008). These reports have included 16 reports of anaphylaxis which met the Brighton case definition for anaphylaxis (Rüggeberg J et al., 2007), and 133 reports of urticarial reactions (or hives). The current estimated rate of anaphylaxis based on doses given in Australia is 2.6 per million. The rate of anaphylaxis following Quadrivalent vaccine based on data from Vaccine Safety Data link in this study was 1.7 cases per million (Gee et al., 2011). 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 (Bohkle et al., 2003).

In the United Kingdom, the Commission on Human Medicines (CHM) considered the MHRA's safety review of Bivalent vaccine and concluded that no serious new risks have been identified during its extensive use in the UK over 2 years, and that the balance of its benefits and risks remains positive. Similarly reassuring data on Bivalent vaccine was obtained in Italy (Gasparini, 2011), Malaysia (ADRAC Bulletin, 2011), and the Netherlands (van Klooster et al., 2011).

Other safety issues

HPV vaccine in combination with other vaccines. Assessment of concomitant use of the Quadrivalent vaccine and recombinant Hepatitis B vaccine showed no increase in adverse events (Reisinger et al., 2010). Concomitant use of the Bivalent vaccine with combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine to girls and young women. was generally well tolerated (Garcia-Sicilia et al., 2010).

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 Quadrivalent human papillomavirus vaccine to women who became pregnant during the phase III clinical trials did not appear to negatively affect pregnancy outcomes (Garland et al., 2009). A pooled analysis of two randomized controlled trials on the risk of miscarriage with Bivalent 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 (Dana et al., 2009). 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 (Forinash AB et al., 2011)

Syncope in adolescent girls. Post-marketing surveillance has documented a number of cases of syncope in adolescent girls (CDC, 2008). 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 (Bernard DM et al., 2011).

Summary of mild and severe adverse events - Quadrivalent HPV vaccine

Nature of Adverse event	Description	Rate/doses
Mild	*Local adverse events*	
	Injection site reaction	83 per 100
	Erythema and swelling	25 per 100
	Severe - injection site erythema and/or swelling > 2 inches in size and pain severe	5.7 per 100
	Systemic adverse events;	
	Pyrexia	13 per 100
	Urticaria	3 per 100
	Headache	26 per 100
	Myalgia	2 per 100
	Arthalgia	1 per 100
	Gastrointestinal disorders	17 per 100
Severe	Anaphylaxis	1.7 – 2.6 per 10^6

Source: European Public Assessment Report (EMEA CHMP, 2006)

Summary of mild and severe adverse events - Bivalent HPV vaccine

Nature of Adverse event	Description	Rate/doses
Generally mild	*Local adverse events*	
	Injection site pain[2]	78 per 100
	Swelling [2]	26 per 100
	Redness	30 per 100
	Systemic adverse events;	
	Fatigue[2]	33 per 100
	Headache[2]	30 per 100
	Myalgia[2]	28 per 100
	Itching[1]	9 per 100
	Arthalgia[2]	10 per 100
	Gastrointestinal symptoms[2]	13 per 100
	Fever [1]	3 per 100
	Rash [1]	1 per 100
	Urticaria [1]	0.46 per 100

Source: Gasparini et al. (2011)[1]; European Public assessment report, EMEA CHMP (2006) [2]

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such (Plotkin et al., 2008, Institute of Medicine of the National Academies 2011) and from data derived from a literature search on Pubmed in 2008 using key words “vaccine antigen”, “Safety” and “adverse events”. An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomized controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: **http://www.who.int/vaccine_safety/vaccrates/en/index.html**

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