

Suspected Adverse Reaction Analysis

Human papillomavirus (HPV) vaccine (brand unspecified)

03 December 2009

This report summarises the reports of adverse reactions suspected to have been caused by human papillomavirus (HPV) vaccine for which information on the specific brand administered (whether Cervarix or Gardasil) is currently unavailable. This includes reports received up to 02 December 2009. Separate Adverse Reaction Analysis summaries exist for reports in which the brand was stated. These reports have been voluntarily submitted to the MHRA by healthcare professionals and members of the public via the Yellow Card Scheme (visit www.yellowcard.gov.uk) and by the manufacturers of the vaccine as part of their legal requirements.

It is essential to bear in mind that reports to the MHRA relate only to adverse medical events which the reporter considered could have been caused by the vaccine (i.e. if there was merely a **suspicion** of causality). Therefore, cases may be true side-effects or they may have been purely coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of vaccination. Events may also have been psychogenic¹ in origin. This report therefore cannot be considered to represent a list of known side-effects of the vaccine. These data also cannot be used to determine the frequency, or incidence, of known side-effects because they are often under-reported. The known side-effects, and their frequencies (based on clinical trial data), are available in the product information (see <http://emc.medicines.org.uk/>).

The reactions in this report have been broken down into 5 categories based on scientific assessment of individual cases by MHRA assessors: injection-site reactions; allergic reactions; 'psychogenic' events; other recognised reactions; and 'suspected adverse reactions not currently recognised' (reactions in this latter category are divided into the high-level classification of System Organ Class)². The same event term may appear in more than one category (e.g. 'rash' may be associated with injection site, allergic or unrecognised suspected reactions and 'psychogenic' events). However, an event from a single report will appear in only one category.

A single report may contain more than one reaction, more than one sign or symptom of a single reaction or different reactions in more than one of the above categories. Therefore the total number of listed reactions is greater than the total number of reports and total reports in each of the 5 tables should not be added together.

Headline summary:

To date, most suspected ADRs reported to MHRA in association with HPV vaccine have related to the signs and symptoms of recognised side effects listed in the product information or were due to the injection process and not the vaccine itself (i.e. 'psychogenic' in nature).

For the isolated case of other medical conditions reported, the available evidence does not suggest that the vaccine caused the condition and these may have been coincidental events.

Following administration of more than 1.4 million doses across the UK since last September, the balance of risks and benefits of Cervarix remains positive

¹ For this analysis, defined as non-allergic events which occurred within minutes of, or soon after, vaccination and were most likely a psychogenic response to, or anticipation of, the injection. These are not side effects to the vaccine as such and can occur with any needle injection procedure.

² Using MedDRA terminology

SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 171

Total number of suspected reactions: 503

Estimated number of doses of Cervarix administered across the UK: at least 1.4 million doses³

A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised⁴ side-effects of HPV vaccines and are listed in the product information. These may occur at a frequency⁵ of more than 1 in 10 persons vaccinated.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of injection site reactions.

Reported event (Preferred Term ²)	Number of cases
Pain in extremity	9
Injection site erythema	5
Erythema	4
Injection site swelling	4
Musculoskeletal stiffness	4
Oedema peripheral	4
Injection site reaction	3
Pain	3
Injection site coldness	2
Injection site discolouration	2
Pruritus	2
Sensory loss	2
Skin reaction	2
Tenderness	2
Complex regional pain syndrome	1
Feeling hot	1
Injection site anaesthesia	1
Injection site haemorrhage	1
Injection site mass	1
Injection site rash	1
Local reaction	1
Local swelling	1
Mobility decreased	1
Musculoskeletal pain	1
Paraesthesia	1
Peripheral coldness	1
Rash	1
Skin discolouration	1
Urticaria	1
Total reactions	63
Total reports	35

³ Based on UK-wide vaccine uptake data to July 2009. As the Yellow Card data are up to the present date, the available uptake data should not be used to derive adverse reaction reporting rates (as this will result in an over-estimation)

⁴ Known to be associated with either Cervarix or Gardasil

⁵ Based on clinical trial data

B. Allergic reactions (including skin reactions not directly related to an injection-site reaction)

Allergic reactions are a recognised⁴ side-effect of HPV vaccines and are listed in the product information. These may occur at a frequency⁵ between 1 in 10 persons (for non-serious types of allergic reaction such as rash and itching) to less than 1 in 10,000 persons vaccinated. Severe allergic reactions are very rare.

The cases reported to the MHRA during use of the vaccine in the UK do not indicate any change in the severity or nature of allergic reactions.

Reported event (Preferred Term ²)	Number of cases
Rash	8
Urticaria	6
Eyelid oedema	4
Erythema	3
Hypersensitivity	3
Rash pruritic	3
Anaphylactic reaction	2
Lip swelling	2
Pharyngeal oedema	2
Rash erythematous	2
Blister	1
Dizziness	1
Dysphagia	1
Dyspnoea	1
Eczema	1
Heat rash	1
Laryngeal oedema	1
Paraesthesia oral	1
Pruritus	1
Rash generalised	1
Rash macular	1
Somnolence	1
Stridor	1
Swelling	1
Swelling face	1
Throat irritation	1
Throat tightness	1
Vomiting	1
Total reactions	53
Total reports	32

C. 'Psychogenic' events

Psychogenic events including vasovagal syncope, faints and panic attacks can occur with any injection procedure, not just vaccination, and can be common in adolescents. These are due to fear and/or anticipation of the needle injection and are not side-effects of HPV vaccine as such. Such events can be associated with a wide range of temporary signs and symptoms including loss of consciousness, vision disturbance, injury, limb jerking (often misinterpreted as a seizure/convulsion), limb numbness or tingling, difficulty in breathing, hyperventilation etc.

Reported event (Preferred Term ²)	Number of cases
Syncope	23
Dizziness	12
Headache	8
Pallor	4
Nausea	3
Rash	3
Somnolence	3
Vomiting	3
Blood pressure increased	2
Convulsion	2
Dyspnoea	2
Heart rate increased	2
Malaise	2
Presyncope	2
Vision blurred	2
Abasia	1
Abdominal discomfort	1
Abdominal pain	1
Asthenia	1
Back pain	1
Blindness transient	1
Body temperature decreased	1
Dyskinesia	1
Heart rate irregular	1
Hot flush	1
Hyperventilation	1
Hypoaesthesia	1
Muscular weakness	1
Paraesthesia	1
Pruritus	1
Sensory loss	1
Urticaria	1
Visual impairment	1
Total reactions	91
Total reports	38

D. 'Other recognised' reactions

This section includes other events recognised⁴ to be side-effects of HPV vaccine and not already included in sections A and B above. This also includes signs and symptoms of recognised side effects. The frequencies, where known, are listed in the product information.

The cases reported to the MHRA during use of the vaccine in the UK so far do not indicate any change in the severity or nature of these reactions.

Reported event (Preferred Term ²)	Number of cases
Nausea	17
Headache	15
Pyrexia	13
Malaise	11
Vomiting	9
Fatigue	6
Dizziness	5
Abdominal pain	3
Abdominal pain upper	3
Lethargy	3
Somnolence	3
Asthenia	2
Body temperature increased	2
Diarrhoea	2
Limb discomfort	2
Musculoskeletal stiffness	2
Myalgia	2
Abdominal pain lower	1
Back pain	1
Body temperature fluctuation	1
Decreased appetite	1
Dysstasia	1
Gastrointestinal disorder	1
Lymphadenopathy	1
Neck pain	1
Oropharyngeal pain	1
Pain	1
Respiratory tract infection	1
Total reactions	111
Total reports	46

E. 'Suspected adverse reactions not currently recognised'

This section includes reports which, based on MHRA assessment of the case details provided, do not fit into one of the above 4 categories.

These suspected ADRs are not currently recognised as side effects of Cervarix vaccine and the available evidence does not suggest a causal link with the vaccine. These are isolated medical events which may have been coincidental with vaccination. These reports are continually assessed by the MHRA.

System Organ Class	Reported event (Preferred Term ²)	Number of cases
Ear and labyrinth disorders	Ear pain	2
	Hyperacusis	1
Endocrine disorders	Adrenocortical insufficiency acute	1
Eye disorders	Diplopia	1
	Eye discharge	1
	Eye pain	1
	Photopsia	1
	Vision blurred	4
	Visual impairment	2
Gastrointestinal disorders	Abdominal discomfort	1
	Abdominal pain	4
	Abdominal pain upper	1
	Diarrhoea	1
	Gingival disorder	1
	Nausea	3
	Oedema mouth	1
	Vomiting	2
General disorders and administration site conditions	Abasia	2
	Chest pain	1
	Chills	1
	Discomfort	1
	Exercise tolerance decreased	1
	Fatigue	7
	Feeling abnormal	1
	Feeling cold	1
	Gait disturbance	1
	Influenza like illness	8
	Injection site haematoma	1
	Local swelling	1
	Malaise	1
	Oedema peripheral	1
	Pain	1
	Pyrexia	4
	Temperature intolerance	1
	Tenderness	1
Thirst	1	
Infections and infestations	Herpes zoster	1
	Labyrinthitis	1
	Skin infection	1
Injury, poisoning and	Axillary nerve injury	1

procedural complications	Contusion	1
Investigations	Body temperature increased	1
Metabolism and nutrition disorders	Diabetes mellitus inadequate control	1
	Hyperglycaemia	1
Musculoskeletal and connective tissue disorders	Arthralgia	4
	Back pain	1
	Joint stiffness	1
	Muscle twitching	1
	Muscular weakness	2
	Musculoskeletal stiffness	1
	Pain in extremity	1
Nervous system disorders	Balance disorder	1
	Cerebellar ataxia	1
	Chorea	1
	Complex regional pain syndrome	1
	Convulsion	2
	Dizziness	9
	Dizziness postural	3
	Dyskinesia	1
	Epilepsy	3
	Grand mal convulsion	1
	Guillain-Barre syndrome	1
	Headache	10
	Hypoaesthesia	4
	Ivth nerve paralysis	1
	Lethargy	4
	Loss of consciousness	3
	Migraine	1
	Neuritis	1
	Paraesthesia	5
	Sensory loss	1
	Somnolence	1
Syncope	4	
Tremor	3	
Psychiatric disorders	Confusional state	2
	Depression	1
	Dissociation	1
	Insomnia	1
Renal and urinary disorders	Neurogenic bladder	1
	Urinary retention	2
Reproductive system and breast disorders	Menstruation delayed	1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1
	Nasal congestion	1
	Oropharyngeal pain	1
	Wheezing	1
Skin and subcutaneous tissue disorders	Acne	1
	Alopecia	2
	Alopecia areata	1
	Erythema	1
	Erythema multiforme	1

	Henoch-Schonlein purpura	1
	Hyperhidrosis	1
	Hypoaesthesia facial	1
	Livedo reticularis	1
	Petechiae	1
	Photosensitivity reaction	1
	Purpura	2
	Rash	4
	Rash erythematous	1
	Rash macular	1
	Skin disorder	1
	Urticaria	1
Vascular disorders	Pallor	2
	Peripheral coldness	3
Total reactions		185
Total reports		61