

## Suspected Adverse Reaction Analysis

### CERVARIX Human papillomavirus (HPV) vaccine

2 July 2009

This report summarises the adverse reactions suspected to have been caused by Cervarix human papillomavirus (HPV) vaccine in the UK. This includes reports received between 14 April 2008 and 1 July 2009. 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](http://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 psychogenic<sup>1</sup> 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)<sup>2</sup>. 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, the vast majority of suspected adverse reactions reported to MHRA in association with Cervarix vaccine have related either 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 cases 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 million doses across the UK since last September, the balance of risks and benefits of Cervarix remains positive.**

<sup>1</sup> 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.

<sup>2</sup> Using MedDRA terminology

## SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 1,913

Total number of suspected reactions: 4,229

Estimated number of doses administered across the UK: at least 1 million doses<sup>3</sup>

### A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised side-effects of Cervarix vaccine and are listed in the product information. These may occur at a frequency<sup>4</sup> of more than 1 in 10 persons vaccinated. The reported cases of 'Pain in extremity' mainly relate to a sore arm.

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 <sup>2</sup> )	Number of cases
Pain in extremity	186
Injection site swelling	53
Limb discomfort	49
Injection site pain	45
Hypoaesthesia	41
Injection site erythema	40
Oedema peripheral	33
Erythema	19
Injection site rash	17
Skin discolouration	14
Injection site reaction	11
Local reaction	11
Pain	11
Injection site mass	10
Musculoskeletal stiffness	9
Paraesthesia	7
Peripheral coldness	7
Rash macular	7
Contusion	6
Injection site pruritus	6
Injection site warmth	6
Local swelling	6
Injection site inflammation	5
Injection site induration	4
Sensation of heaviness	4
Sensory disturbance	4
Feeling cold	3
Injection site anaesthesia	3
Injection site discharge	3
Injection site haematoma	3
Limb immobilisation	3
Muscular weakness	3
Myalgia	3
Asthenia	2

<sup>3</sup> Based on UK-wide vaccine uptake data to March 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)

<sup>4</sup> Based on clinical trial data

Feeling hot	2
Inflammation	2
Injection site infection	2
Injection site urticaria	2
Injection site vesicles	2
Poor peripheral circulation	2
Pruritus	2
Sensory loss	2
Cyanosis	1
Grip strength decreased	1
Immobile	1
Injection site discolouration	1
Injection site haemorrhage	1
Injection site irritation	1
Injection site joint pain	1
Injection site papule	1
Injection site paraesthesia	1
Musculoskeletal pain	1
Neck pain	1
Pallor	1
Rash pruritic	1
Scab	1
Sensation of pressure	1
Swelling	1
Tenderness	1
Urticaria	1
Total reactions	668
Total reports	483

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

Allergic reactions are recognised side-effect of Cervarix vaccine and are listed in the product information. These may occur at a frequency<sup>4</sup> 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 <sup>2</sup> )	Number of cases
Rash	60
Urticaria	35
Pruritus	26
Rash pruritic	20
Swelling face	19
Oedema peripheral	18
Erythema	15
Rash macular	15
Rash generalised	12
Dyspnoea	11
Hypersensitivity	11

Eye swelling	10
Lip swelling	10
Anaphylactic reaction	9
Paraesthesia oral	9
Dizziness	6
Pallor	5
Pruritus generalised	5
Throat tightness	5
Paraesthesia	4
Pharyngeal oedema	4
Rash erythematous	4
Flushing	3
Dysphagia	2
Eye pruritus	2
Feeling hot	2
Heart rate increased	2
Hyperhidrosis	2
Hyperventilation	2
Malaise	2
Nasopharyngitis	2
Ocular hyperaemia	2
Peripheral coldness	2
Purpura	2
Rash maculo-papular	2
Skin irritation	2
Syncope	2
Throat irritation	2
Wheezing	2
Angioedema	1
Blister	1
Body temperature increased	1
Chest discomfort	1
Cold sweat	1
Conjunctival hyperaemia	1
Deafness	1
Dermatitis	1
Dermatitis allergic	1
Eczema	1
Eyelid oedema	1
Fatigue	1
Feeling abnormal	1
Generalised erythema	1
Gingival swelling	1
Hypersomnia	1
Hypertension	1
Hypoaesthesia	1
Limb discomfort	1
Musculoskeletal stiffness	1
Nausea	1
Neck pain	1
Pain in extremity	1
Periorbital oedema	1
Petechiae	1
Respiratory rate increased	1

Skin reaction	1
Sneezing	1
Speech disorder	1
Swelling	1
Swollen tongue	1
Tachycardia	1
Tremor	1
Type I hypersensitivity	1
Vomiting	1
Total reactions	383
Total reports	224

### 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 Cervarix 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.

The events in the list below were considered 'psychogenic' in nature based on MHRA assessment of the individual case details reported. The reported cases which do not refer specifically to vasovagal syncope, faint or panic attack (e.g. convulsion, transient blindness which refers to temporary loss of vision at the start of a faint) were concurrently reported as signs or symptom of the psychogenic event; **i.e. these also were not side-effects of the vaccine itself.**

Reported event (Preferred Term <sup>2</sup> )	Number of cases
Dizziness	162
Syncope	158
Nausea	80
Headache	69
Pallor	59
Malaise	44
Tremor	33
Vomiting	33
Flushing	26
Vision blurred	24
Feeling hot	23
Cold sweat	22
Presyncope	13
Paraesthesia	12
Hyperhidrosis	11
Loss of consciousness	11
Rash	10
Chills	8
Dyskinesia	8
Dyspnoea	8
Muscle twitching	8
Pyrexia	8
Unresponsive to stimuli	8

Eye rolling	7
Heart rate increased	7
Hyperventilation	7
Somnolence	7
Tearfulness	7
Asthenia	6
Convulsion	6
Erythema	6
Hypoaesthesia	6
Muscle rigidity	6
Visual impairment	6
Abdominal pain upper	5
Chest discomfort	5
Fatigue	5
Feeling cold	5
Feeling of body temperature change	5
Nervousness	5
Panic attack	5
Rash macular	5
Tachycardia	5
Throat tightness	5
Abdominal pain	4
Blindness transient	4
Confusional state	4
Dysgeusia	4
Feeling abnormal	4
Muscular weakness	4
Mydriasis	4
Peripheral coldness	4
Body temperature increased	3
Fall	3
Hypotension	3
Lethargy	3
Muscle spasms	3
Nasopharyngitis	3
Pain	3
Pulse abnormal	3
Abasia	2
Abdominal discomfort	2
Amnesia	2
Anxiety	2
Bradycardia	2
Chest pain	2
Disorientation	2
Disturbance in attention	2
Dizziness postural	2
Dysarthria	2
Dysphagia	2
Heart rate irregular	2
Hot flush	2
Hypertension	2
Musculoskeletal stiffness	2
Myalgia	2
Neck pain	2

Pain in extremity	2
Photophobia	2
Pruritus	2
Respiratory rate increased	2
Retching	2
Salivary hypersecretion	2
Sensory loss	2
Skin discolouration	2
Throat irritation	2
Tinnitus	2
Urticaria	2
Agitation	1
Altered state of consciousness	1
Anorexia	1
Balance disorder	1
Blood pressure decreased	1
Bruxism	1
Burning sensation	1
Cough	1
Cyanosis	1
Deafness	1
Deafness transitory	1
Depressed level of consciousness	1
Discomfort	1
Dry mouth	1
Dry throat	1
Dysstasia	1
Ear pain	1
Eyelid oedema	1
Face injury	1
Facial spasm	1
Feeling drunk	1
Feeling of despair	1
Grand mal convulsion	1
Head discomfort	1
Hearing impaired	1
Hypersomnia	1
Hypoacusis	1
Hypokinesia	1
Lip swelling	1
Livedo reticularis	1
Migraine	1
Nervous system disorder	1
Oropharyngeal pain	1
Palpitations	1
Panic reaction	1
Procedural dizziness	1
Psychomotor hyperactivity	1
Pupil fixed	1
Rash generalised	1
Respiratory arrest	1
Respiratory rate decreased	1
Seizure anoxic	1
Sensation of heaviness	1

Shock	1
Sinus tachycardia	1
Sleep attacks	1
Vertigo	1
Total reactions	1118
Total reports	424

#### D. 'Other recognised' reactions

This section includes other events recognised to be side-effects of Cervarix 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 <sup>2</sup> )	Number of cases
Nausea	294
Headache	292
Dizziness	258
Vomiting	114
Malaise	93
Fatigue	81
Pyrexia	79
Abdominal pain	38
Abdominal pain upper	30
Myalgia	28
Diarrhoea	23
Feeling hot	20
Body temperature increased	19
Arthralgia	18
Pain	16
Lethargy	14
Chills	11
Oropharyngeal pain	10
Pallor	10
Paraesthesia	10
Abdominal discomfort	8
Somnolence	8
Influenza like illness	6
Musculoskeletal stiffness	6
Pain in extremity	6
Pruritus	6
Asthenia	5
Back pain	3
Flushing	3
Hypoaesthesia	3
Neck pain	3
Tremor	3
Anorexia	2
Cough	2

Feeling cold	2
Head discomfort	2
Joint swelling	2
Listless	2
Photophobia	2
Rash	2
Skin warm	2
Syncope	2
Abdominal pain lower	1
Body temperature fluctuation	1
Erythema	1
Feeling of body temperature change	1
Hot flush	1
Hyperhidrosis	1
Ill-defined disorder	1
Induration	1
Insomnia	1
Local swelling	1
Loss of consciousness	1
Lower respiratory tract infection	1
Migraine	1
Muscle spasms	1
Muscle twitching	1
Muscular weakness	1
Musculoskeletal chest pain	1
Musculoskeletal pain	1
Nasal congestion	1
Nervousness	1
Peripheral coldness	1
Pharyngitis	1
Pruritus generalised	1
Psoriasis	1
Respiratory disorder	1
Restlessness	1
Thirst	1
Upper respiratory tract infection	1
Urticaria	1
Total reactions	1567
Total reports	845

### 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.

Guillain Barre Syndrome (GBS) naturally occurs in the population and is usually thought to be caused by a preceding infectious illness. Several hundred thousand doses of Cervarix have been given to girls and there is no evidence that the vaccine has increased the frequency of GBS above that expected to occur naturally in the population.

System Organ Class	Reported event (Preferred Term <sup>2</sup> )	Number of cases
Blood and lymphatic system disorders	Eosinophilia	1
	Lymphadenopathy	11
Cardiac disorders	Cyanosis	1
	Palpitations	3
	Sinus tachycardia	1
	Tachycardia	1
Ear and labyrinth disorders	Deafness	1
	Deafness bilateral	1
	Ear pain	6
	Tinnitus	1
Eye disorders	Dry eye	1
	Excessive eye blinking	1
	Eye swelling	1
	Photophobia	1
	Vision blurred	6
	Visual impairment	3
Gastrointestinal disorders	Abdominal pain lower	1
	Abdominal pain upper	1
	Abnormal faeces	1
	Colitis ulcerative	1
	Constipation	1
	Diarrhoea	4
	Flatulence	1
	Lip swelling	1
	Mouth ulceration	1
	Nausea	9
	Vomiting	8
	General disorders and administration site conditions	Abasia
Asthenia		1
Axillary pain		1
Chest discomfort		3
Chest pain		10
Chills		3
Chronic fatigue syndrome		1
Fatigue		6
Feeling abnormal		2
Feeling cold		5

	Feeling hot	1
	Gait disturbance	2
	Influenza like illness	18
	Injection site reaction	1
	Local swelling	1
	Malaise	7
	Oedema peripheral	3
	Pain	6
	Pyrexia	4
	Sensation of foreign body	1
	Sensation of pressure	1
	Swelling	1
	Thirst	1
Infections and infestations	Acarodermatitis	1
	Application site pustules	1
	Folliculitis	1
	Impetigo	1
	Infectious mononucleosis	1
	Influenza	2
	Kidney infection	1
	Lower respiratory tract infection	2
	Nasopharyngitis	4
	Pneumonia viral	1
	Post viral fatigue syndrome	4
	Streptococcal sepsis	1
	Tonsillitis	1
	Urinary tract infection	2
	Varicella	1
Injury, poisoning and procedural complications	Viral infection	2
	Contusion	3
Injury, poisoning and procedural complications	Drug exposure during pregnancy	2
Investigations	Blood glucose increased	3
	Blood pressure abnormal	1
	Blood pressure increased	1
	Body temperature increased	1
	Respiratory rate increased	1
	Weight decreased	2
Metabolism and nutrition disorders	Anorexia	2
	Decreased appetite	2
	Dehydration	1
	Diabetes mellitus inadequate control	1
	Diabetic ketoacidosis	1
	Hypoglycaemia	1
	Increased appetite	1
	Type 1 diabetes mellitus	1
Musculoskeletal and connective tissue disorders	Arthralgia	5
	Back pain	3
	Bone pain	1
	Flank pain	1

	Muscle spasms	2
	Muscle twitching	2
	Muscular weakness	9
	Musculoskeletal chest pain	1
	Musculoskeletal stiffness	4
	Myalgia	2
	Neck pain	3
	Pain in extremity	15
	Palindromic rheumatism	1
	Sensation of heaviness	1
Nervous system disorders	Ataxia	1
	Burning sensation	1
	Complex regional pain syndrome	1
	Convulsion	10
	Coordination abnormal	1
	Crying	2
	Disturbance in attention	1
	Dizziness	10
	Dizziness postural	1
	Dysarthria	1
	Dysstasia	2
	Epilepsy	3
	Facial palsy	1
	Grand mal convulsion	1
	Guillain-Barre syndrome	1
	Headache	12
	Hemiparesis	1
	Hypoaesthesia	7
	Lethargy	4
	Loss of consciousness	3
	Meningism	1
	Migraine	10
	Migraine with aura	1
	Myoclonic epilepsy	1
	Optic neuritis	1
	Paraesthesia	4
	Paralysis	1
	Psychomotor hyperactivity	1
	Sensory disturbance	3
	Sensory loss	2
	Somnolence	10
Status epilepticus	1	
Syncope	12	
Tremor	3	
Unresponsive to stimuli	1	
Visual field defect	3	
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	4
Psychiatric disorders	Abnormal behaviour	1
	Aggression	1
	Anxiety	1

	Confusional state	2
	Depression	1
	Dysphemia	1
	Eating disorder	1
	Emotional disorder	1
	Fear	1
	Hallucination, visual	1
	Insomnia	3
	Screaming	1
	Sleep disorder	2
	Somatisation disorder	1
Renal and urinary disorders	Urinary incontinence	1
Reproductive system and breast disorders	Amenorrhoea	1
	Breast pain	1
	Breast swelling	1
	Breast tenderness	1
	Menorrhagia	2
	Menstrual disorder	1
	Menstruation irregular	1
	Metrorrhagia	1
	Vaginal discharge	1
	Vaginal haemorrhage	3
	Vulval ulceration	1
Respiratory, thoracic and mediastinal disorders	Asthma	3
	Cough	2
	Dyspnoea	11
	Epistaxis	3
	Haemoptysis	1
	Hypoventilation	1
	Nasal congestion	1
	Oropharyngeal blistering	1
	Oropharyngeal pain	7
	Rhinorrhoea	1
Wheezing	3	
Skin and subcutaneous tissue disorders	Acne	1
	Alopecia	4
	Alopecia areata	1
	Blister	3
	Dermatitis allergic	1
	Eczema	4
	Erythema	2
	Erythema multiforme	2
	Guttate psoriasis	1
	Hyperhidrosis	1
	Hypoaesthesia facial	2
	Rash	3
	Rash maculo-papular	1
	Rash vesicular	1
	Skin discolouration	4
	Skin exfoliation	1
	Skin hypertrophy	1
	Skin lesion	1
Stevens-Johnson	1	

	syndrome	
	Trichorrhexis	1
	Urticaria	2
Vascular disorders	Circulatory collapse	1
	Flushing	1
	Haemorrhage	1
	Hot flush	1
	Hypotension	3
	Pallor	1
	Peripheral coldness	6
Total reactions		493
Total reports		281

In relation to safety in pregnancy, during pre-licensing studies of Cervarix it was found that almost 870 women became pregnant before or after receiving the vaccine. The overall rates of spontaneous abortion in these clinical trials were no greater than the background rates in the general population (i.e. regardless of vaccination). There is currently no evidence to suggest that Cervarix vaccine carries any risks during pregnancy. Nonetheless, Cervarix is not recommended for use in pregnancy.