

Suspected Adverse Reaction Analysis

CERVARIX Human papillomavirus (HPV) vaccine

08 October 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 07 October 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) 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, 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 1.4 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.

²Using MedDRA terminology

SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 2,207

Total number of suspected reactions: 4,863

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

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 frequency⁴ 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 ²)	Number of cases
Pain in extremity	225
Injection site swelling	75
Injection site pain	53
Hypoaesthesia	52
Limb discomfort	52
Injection site erythema	51
Oedema peripheral	40
Erythema	25
Injection site rash	17
Skin discolouration	16
Injection site reaction	15
Local reaction	13
Pain	12
Injection site mass	11
Musculoskeletal stiffness	11
Injection site warmth	10
Injection site inflammation	8
Local swelling	8
Paraesthesia	8
Peripheral coldness	8
Contusion	7
Injection site pruritus	7
Rash macular	7
Injection site induration	6
Asthenia	4
Myalgia	4
Sensation of heaviness	4
Sensory disturbance	4
Feeling cold	3
Injection site anaesthesia	3
Injection site discharge	3
Injection site haematoma	3
Injection site infection	3
Injection site urticaria	3

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 Based on clinical trial data

Limb immobilisation	3
Muscular weakness	3
Poor peripheral circulation	3
Feeling hot	2
Grip strength decreased	2
Inflammation	2
Injection site irritation	2
Injection site vesicles	2
Pallor	2
Pruritus	2
Sensory loss	2
Swelling	2
Cyanosis	1
Immobile	1
Injection site cellulitis	1
Injection site discolouration	1
Injection site haemorrhage	1
Injection site joint pain	1
Injection site movement impairment	1
Injection site papule	1
Injection site paraesthesia	1
Livedo reticularis	1
Muscle spasms	1
Musculoskeletal pain	1
Neck pain	1
Pain of skin	1
Rash	1
Rash maculo-papular	1
Rash pruritic	1
Scab	1
Sensation of pressure	1
Tenderness	1
Tremor	1
Urticaria	1
Total reactions	820
Total reports	585

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 frequency⁴ 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 Term²)	Number of cases
Rash	66
Urticaria	43
Pruritus	28

Swelling face	23
Oedema peripheral	20
Rash pruritic	19
Lip swelling	16
Erythema	15
Rash macular	15
Anaphylactic reaction	14
Dyspnoea	13
Hypersensitivity	12
Rash generalised	12
Eye swelling	11
Paraesthesia oral	10
Dizziness	7
Flushing	5
Pallor	5
Pharyngeal oedema	5
Pruritus generalised	5
Rash erythematous	5
Throat tightness	5
Malaise	4
Paraesthesia	4
Wheezing	4
Angioedema	3
Swollen tongue	3
Anaphylactic shock	2
Blister	2
Chest discomfort	2
Dysphagia	2
Eyelid oedema	2
Eye pruritus	2
Feeling hot	2
Heart rate increased	2
Hyperhidrosis	2
Hyperventilation	2
Hypoaesthesia	2
Nasopharyngitis	2
Nausea	2
Ocular hyperaemia	2
Peripheral coldness	2
Purpura	2
Rash maculo-papular	2
Skin irritation	2
Syncope	2
Throat irritation	2
Vomiting	2
Asthenia	1
Body temperature increased	1
Cold sweat	1
Conjunctival hyperaemia	1
Convulsion	1
Dermatitis	1
Dermatitis allergic	1
Dermatitis contact	1
Eczema	1

Eyes sunken	1
Face oedema	1
Fatigue	1
Feeling abnormal	1
Generalised erythema	1
Gingival swelling	1
Hypersomnia	1
Hypertension	1
Laryngeal oedema	1
Limb discomfort	1
Local swelling	1
Musculoskeletal stiffness	1
Neck pain	1
Oral pain	1
Pain	1
Pain in extremity	1
Periorbital oedema	1
Petechiae	1
Pyrexia	1
Respiratory rate increased	1
Skin disorder	1
Skin reaction	1
Sneezing	1
Speech disorder	1
Swelling	1
Tachycardia	1
Thirst	1
Tremor	1
Type I hypersensitivity	1
Total reactions	452
Total reports	257

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 ²)	Number of cases
Syncope	185
Dizziness	172
Nausea	88

Headache	73
Pallor	64
Malaise	45
Vomiting	39
Tremor	34
Flushing	28
Feeling hot	25
Vision blurred	25
Cold sweat	23
Hyperhidrosis	15
Presyncope	15
Loss of consciousness	14
Paraesthesia	13
Convulsion	11
Rash	10
Dyspnoea	9
Pyrexia	9
Unresponsive to stimuli	9
Asthenia	8
Chills	8
Eye rolling	8
Heart rate increased	8
Hyperventilation	8
Muscle twitching	8
Panic attack	8
Dyskinesia	7
Fatigue	7
Hypoaesthesia	7
Somnolence	7
Tearfulness	7
Erythema	6
Feeling of body temperature change	6
Muscle rigidity	6
Rash macular	6
Tachycardia	6
Visual impairment	6
Abdominal pain upper	5
Chest discomfort	5
Dysgeusia	5
Feeling cold	5
Lethargy	5
Nervousness	5
Throat tightness	5
Abdominal pain	4
Blindness transient	4
Confusional state	4
Fall	4
Feeling abnormal	4
Muscular weakness	4
Mydriasis	4
Peripheral coldness	4
Anorexia	3
Body temperature increased	3
Deafness	3

Feeling drunk	3
Hypotension	3
Muscle spasms	3
Musculoskeletal stiffness	3
Nasopharyngitis	3
Pain	3
Pulse abnormal	3
Skin discolouration	3
Urticaria	3
Abasia	2
Abdominal discomfort	2
Amnesia	2
Anxiety	2
Bradycardia	2
Chest pain	2
Diplopia	2
Disorientation	2
Disturbance in attention	2
Dizziness postural	2
Dysarthria	2
Dysphagia	2
Heart rate irregular	2
Hot flush	2
Hypertension	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
Shock	2
Throat irritation	2
Tinnitus	2
Agitation	1
Altered state of consciousness	1
Balance disorder	1
Blood pressure decreased	1
Blood pressure increased	1
Blood pressure systolic decreased	1
Bruxism	1
Burning sensation	1
Consciousness fluctuating	1
Cough	1
Cyanosis	1
Deafness transitory	1
Depressed level of consciousness	1
Discomfort	1
Dry mouth	1
Dry throat	1
Dysstasia	1
Ear discomfort	1

Ear pain	1
Eyelid oedema	1
Face injury	1
Facial spasm	1
Fear	1
Feeling of despair	1
Foaming at mouth	1
Grand mal convulsion	1
Head discomfort	1
Hearing impaired	1
Heart rate decreased	1
Hypersomnia	1
Hypoacusis	1
Hypokinesia	1
Lip swelling	1
Livedo reticularis	1
Migraine	1
Myoclonus	1
Nervous system disorder	1
Oropharyngeal pain	1
Palpitations	1
Panic reaction	1
Poor peripheral circulation	1
Procedural dizziness	1
Psychomotor hyperactivity	1
Pupil fixed	1
Rash generalised	1
Respiratory arrest	1
Respiratory rate decreased	1
Road traffic accident	1
Seizure anoxic	1
Sensation of heaviness	1
Sinus tachycardia	1
Sleep attacks	1
Urinary incontinence	1
Vertigo	1
Total reactions	1244
Total reports	479

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 ²)	Number of cases
Headache	323
Nausea	308
Dizziness	275
Vomiting	131
Malaise	98
Fatigue	97
Pyrexia	94
Abdominal pain	43
Abdominal pain upper	32
Myalgia	31
Diarrhoea	26
Arthralgia	22
Feeling hot	21
Body temperature increased	20
Lethargy	17
Pain	16
Paraesthesia	13
Chills	11
Oropharyngeal pain	11
Somnolence	11
Pallor	10
Abdominal discomfort	8
Asthenia	7
Pruritus	7
Influenza like illness	6
Musculoskeletal stiffness	6
Pain in extremity	6
Neck pain	4
Back pain	3
Flushing	3
Hypoaesthesia	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
Abdominal pain lower	1
Body temperature fluctuation	1

Erythema	1
Feeling of body temperature change	1
Gait disturbance	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	1714
Total reports	928

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.

Chronic fatigue syndrome (CFS) is not an uncommon condition amongst adolescents and rates are greater in females than in males. Given that more than 1 million doses of Cervarix have now been given in the UK, it is inevitable that conditions such as CFS will occur not long after vaccination regardless of any causal association with the vaccine.

MHRA has conducted an analysis of reported cases of CFS compared to the normal background frequency. This analysis shows that amongst the population of 12-13 yr old girls immunised so far

in the UK, we would have expected to observe more than 70 new cases of CFS already, regardless of vaccination. We would also expect to have seen many more cases of chronic fatigue-like syndrome that have not necessarily met the diagnostic criteria for CFS amongst this population.

The Government's independent expert advisory Committee on vaccines and medicines safety, the Commission on Human Medicines (CHM), recently reviewed the cases of CFS, post-viral fatigue syndrome and cases that could possibly represent a chronic fatigue-like syndrome. They advised that the available evidence does not support a causal association between Cervarix vaccine and CFS, and the balance of risks and benefits of Cervarix remains positive. Cases of possible CFS will remain under close and continual review by the MHRA.

System Organ Class	Reported event (Preferred Term ²)	Number of cases
Blood and lymphatic system disorders	Anaemia	1
	Eosinophilia	1
	Lymphadenopathy	12
Cardiac disorders	Cyanosis	1
	Palpitations	3
	Sinus tachycardia	1
	Tachycardia	1
Congenital, familial and genetic disorders	Arteriovenous malformation	1
Ear and labyrinth disorders	Deafness	1
	Deafness bilateral	1
	Ear pain	6
	Tinnitus	1
Eye disorders	Diplopia	1
	Dry eye	1
	Excessive eye blinking	1
	Eye pain	1
	Eye swelling	1
	Mydriasis	1
	Myodesopsia	1
	Photophobia	1
	Vision blurred	6
	Visual impairment	3
	Gastrointestinal disorders	Abdominal pain
Abdominal pain lower		1
Abdominal pain upper		1
Abnormal faeces		1
Colitis ulcerative		1
Constipation		1
Diarrhoea		4
Flatulence		1
Frequent bowel movements		1
Gastrointestinal disorder		1
Hypoaesthesia oral		1
Lip swelling		1
Mouth ulceration		2
Nausea		14
Vomiting		8

General disorders and administration site conditions	Abasia	3	
	Asthenia	2	
	Axillary pain	1	
	Chest discomfort	4	
	Chest pain	9	
	Chills	3	
	Chronic fatigue syndrome	2	
	Condition aggravated	1	
	Fatigue	8	
	Feeling abnormal	2	
	Feeling cold	4	
	Feeling hot	1	
	Gait disturbance	2	
	Inflammation	1	
	Influenza like illness	25	
	Injection site reaction	1	
	Local swelling	1	
	Malaise	8	
	Oedema peripheral	3	
	Pain	9	
	Pyrexia	5	
	Sensation of foreign body	1	
	Sensation of pressure	1	
	Swelling	1	
	Thirst	1	
	Infections and infestations	Abscess	1
		Acarodermatitis	1
		Application site pustules	1
Folliculitis		1	
Furuncle		1	
Herpes zoster		1	
Impetigo		1	
Infectious mononucleosis		1	
Influenza		2	
Kidney infection		1	
Lower respiratory tract infection		3	
Nasopharyngitis		4	
Pharyngitis		1	
Pneumonia viral		1	
Post viral fatigue syndrome		4	
Staphylococcal infection		1	
Streptococcal sepsis		1	
Tonsillitis		1	
Urinary tract infection		2	
Varicella		1	
Viral infection	2		
Injury, poisoning and procedural complications	Contusion	4	
	Drug exposure during pregnancy	3	
	Wrong technique in drug usage process	1	
Investigations	Blood glucose increased	3	

	Blood pressure abnormal	1
	Blood pressure increased	1
	Body temperature increased	1
	Cell marker increased	1
	Heart rate decreased	1
	Neutrophil count decreased	1
	Respiratory rate increased	1
	Weight decreased	2
	Weight increased	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	10
	Arthritis	1
	Arthritis reactive	1
	Back pain	3
	Bone pain	1
	Flank pain	1
	Groin pain	1
	Muscle spasms	2
	Muscle twitching	2
	Muscular weakness	9
	Musculoskeletal chest pain	1
	Musculoskeletal pain	1
	Musculoskeletal stiffness	4
	Myalgia	4
	Neck pain	4
	Pain in extremity	17
	Palindromic rheumatism	1
	Rheumatoid arthritis	1
	Sensation of heaviness	1
	Weight bearing difficulty	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Benign hydatidiform mole	1
	Neoplasm malignant	1
Nervous system disorders	Ataxia	1
	Complex regional pain syndrome	1
	Convulsion	14
	Coordination abnormal	1
	Crying	2
	Diplegia	2
	Disturbance in attention	1

	Dizziness	14
	Dizziness postural	1
	Dysarthria	2
	Dysgeusia	1
	Dysstasia	3
	Encephalitis	1
	Epilepsy	3
	Facial palsy	1
	Grand mal convulsion	5
	Guillain-Barre syndrome	1
	Headache	23
	Hypoaesthesia	9
	Lethargy	6
	Loss of consciousness	6
	Meningism	1
	Migraine	10
	Migraine with aura	1
	Monoplegia	1
	Myoclonic epilepsy	1
	Optic neuritis	1
	Paraesthesia	7
	Paralysis	1
	Psychomotor hyperactivity	1
	Sensory disturbance	3
	Sensory loss	1
	Somnolence	10
	Status epilepticus	1
	Syncope	13
	Tremor	5
	Unresponsive to stimuli	1
	Visual field defect	3
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	6
Psychiatric disorders	Abnormal behaviour	1
	Acute psychosis	1
	Aggression	1
	Anxiety	2
	Confusional state	2
	Depression	1
	Dysphemia	1
	Eating disorder	1
	Emotional disorder	2
	Fear	1
	Hallucination	4
	Hallucination, visual	1
	Insomnia	5
	Screaming	1
	Sleep disorder	2
Somatisation disorder	1	
Tearfulness	1	
Renal and urinary disorders	Urinary incontinence	1
Reproductive system and breast disorders	Amenorrhoea	3
	Breast pain	1

	Breast swelling	1
	Breast tenderness	1
	Cervix inflammation	1
	Menorrhagia	2
	Menstrual disorder	1
	Menstruation irregular	1
	Metrorrhagia	1
	Vaginal discharge	1
	Vaginal haemorrhage	4
	Vulval ulceration	1
Respiratory, thoracic and mediastinal disorders	Asthma	4
	Cough	3
	Dyspnoea	16
	Epistaxis	5
	Haemoptysis	2
	Hypoventilation	1
	Increased upper airway secretion	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	2
	Blister	3
	Dermatitis allergic	1
	Eczema	4
	Erythema	2
	Erythema multiforme	4
	Guttate psoriasis	1
	Hyperhidrosis	1
	Hypoaesthesia facial	3
	Rash	3
	Rash generalised	1
	Rash maculo-papular	1
	Rash vesicular	1
	Skin discolouration	3
	Skin exfoliation	2
	Skin hypertrophy	1
	Skin lesion	1
	Stevens-Johnson syndrome	1
Trichorrhexis	1	
Urticaria	2	
Vascular disorders	Circulatory collapse	1
	Deep vein thrombosis	1
	Flushing	1
	Haemorrhage	1
	Hot flush	1
	Hypotension	3
	Pallor	2
	Peripheral coldness	5

Total reactions		633
Total reports		352

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.