Suspected Adverse Reaction Analysis

CERVARIX Human papillomavirus (HPV) vaccine

5 March 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 4 March 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 psychogenic[1] 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.

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: 1,340
Total number of suspected reactions: 2,891
Estimated number of doses administered: at least 700,000 doses[3]

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[4] 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	133
Injection site swelling	33
Injection site erythema	27
Hypoaesthesia	26
Injection site pain	25
Limb discomfort	20
Oedema peripheral	16
Erythema	15
Injection site rash	10
Skin discolouration	10
Injection site reaction	8
Musculoskeletal stiffness	8
Pain	8
Local reaction	7
Injection site mass	6
Injection site inflammation	5
Rash macular	5
Contusion	4
Local swelling	4
Paraesthesia	4
Injection site induration	3
Injection site pruritus	3
Sensation of heaviness	3
Feeling cold	2
Feeling hot	2
Injection site vesicles	2
Injection site warmth	2
Muscular weakness	2
Myalgia	2
Peripheral coldness	2

[3] Based on UK-wide vaccine uptake data to January 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

Pruritus	2
Sensory disturbance	2
Asthenia	1
Cyanosis	1
Grip strength decreased	1
Immobile	1
Inflammation	1
Injection site discharge	1
Injection site infection	1
Injection site irritation	1
Injection site joint pain	1
Injection site papule	1
Injection site urticaria	1
Limb immobilisation	1
Rash pruritic	1
Scab	1
Sensory loss	1
Swelling	1
Urticaria	1
Total reactions	418
Total reports	312

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[4] 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	43
Urticaria	23
Pruritus	21
Rash pruritic	14
Erythema	13
Swelling face	13
Oedema peripheral	12
Rash macular	11
Lip swelling	9
Eye swelling	8
Hypersensitivity	7
Rash generalised	7
Paraesthesia oral	6
Anaphylactic reaction	5

Dyspnoea	5
Paraesthesia	4
Throat tightness	4
Dizziness	3
Pallor	3
Dysphagia	2
Eye pruritus	2
Flushing	2
Ocular hyperaemia	2
Peripheral coldness	2
Pharyngeal oedema	2
Pruritus generalised	2
Purpura	2
Rash erythematous	2
Throat irritation	2
Angioedema	1
Blister	1
Chest discomfort	1
Eyelid oedema	1
Feeling hot	1
Gingival swelling	1
Hyperhidrosis	1
Hypertension	1
Hyperventilation	1
Hypoaesthesia	1
Limb discomfort	1
Malaise	1
Musculoskeletal stiffness	1
Nasopharyngitis	1
Nausea	1
Neck pain	1
Periorbital oedema	1
Petechiae	1
Rash maculo-papular	1
Respiratory rate increased	1
Skin inflammation	1
Sneezing	1
Speech disorder	1
Swelling	1
Swollen tongue	1
Tachycardia	1
Type I hypersensitivity	1
Wheezing	1
Total reactions	259
Total reports	156

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**
Dizziness	129
Syncope	123
Nausea	68
Headache	56
Pallor	43
Malaise	32
Tremor	28
Flushing	23
Vomiting	22
Cold sweat	18
Feeling hot	18
Vision blurred	18
Paraesthesia	11
Syncope vasovagal	11
Hyperhidrosis	8
Loss of consciousness	8
Rash	8
Somnolence	7
Chills	6
Dyskinesia	6
Heart rate increased	6
Hypoaesthesia	6
Tearfulness	6
Unresponsive to stimuli	6
Abdominal pain upper	5
Asthenia	5
Convulsion	5
Erythema	5
Eye rolling	5
Fatigue	5
Feeling cold	5
Feeling of body temperature change	5
Muscle rigidity	5

Muscle twitching	5
Visual impairment	5
Blindness transient	4
Dyspnoea	4
Feeling abnormal	4
Muscular weakness	4
Nervousness	4
Rash macular	4
Abdominal pain	3
Chest discomfort	3
Confusional state	3
Hyperventilation	3
Nasopharyngitis	3
Panic attack	3
Peripheral coldness	3
Tachycardia	3
Abasia	2
Anxiety	2
Disturbance in attention	2
Dizziness postural	2
Dysgeusia	2
Hot flush	2
Hypertension	2
Muscle spasms	2
Myalgia	2
Mydriasis	2
Neck pain	2
Pulse abnormal	2
Retching	2
Skin discolouration	2
Stomach discomfort	2
Tinnitus	2
Altered state of consciousness	1
Body temperature increased	1
Bruxism	1
Burning sensation	1
Chest pain	1
Cyanosis	1
Deafness	1
Deafness transitory	1
Discomfort	1
Disorientation	1
Dry mouth	1
Dry throat	1
Dysphagia	1
Dysstasia	1
Ear pain	1
Eyelid oedema	1
Face injury	1
Facial spasm	1
Fall	1

Feeling of despair	1
Grand mal convulsion	1
Head discomfort	1
Heart rate irregular	1
Hypersomnia	1
Lethargy	1
Lip swelling	1
Livedo reticularis	1
Musculoskeletal stiffness	1
Nervous system disorder	1
Oropharyngeal pain	1
Pain	1
Pain in extremity	1
Palpitations	1
Panic reaction	1
Photophobia	1
Pruritus	1
Pyrexia	1
Rash generalised	1
Respiratory arrest	1
Respiratory rate decreased	1
Respiratory rate increased	1
Salivary hypersecretion	1
Seizure anoxic	1
Sensation of heaviness	1
Sensory loss	1
Shock	1
Throat irritation	1
Throat tightness	1
Urticaria	1
Total reactions	851
Total reports	330

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
Nausea	227
Headache	212
Dizziness	210
Vomiting	76
Malaise	71
Fatigue	60
Pyrexia	36
Abdominal pain upper	26
Abdominal pain	24
Feeling hot	16
Myalgia	14
Diarrhoea	12
Pain	10
Arthralgia	9
Body temperature increased	9
Lethargy	9
Paraesthesia	8
Oropharyngeal pain	7
Pallor	7
Stomach discomfort	7
Chills	6
Somnolence	6
Pain in extremity	5
Influenza like illness	4
Musculoskeletal stiffness	4
Pruritus	4
Flushing	3
Neck pain	3
Asthenia	2
Back pain	2
Head discomfort	2
Hypoaesthesia	2
Listless	2
Rash	2
Skin warm	2
Abdominal discomfort	1
Abdominal pain lower	1
Anorexia	1
Body temperature fluctuation	1
Cough	1

Erythema	1
Feeling of body temperature change	1
Hot flush	1
Ill-defined disorder	1
Induration	1
Local swelling	1
Lower respiratory tract infection	1
Migraine	1
Muscle twitching	1
Musculoskeletal chest pain	1
Musculoskeletal pain	1
Nasal congestion	1
Nervousness	1
Peripheral coldness	1
Pharyngitis	1
Pruritus generalised	1
Respiratory disorder	1
Thirst	1
Tremor	1
Upper respiratory tract infection	1
Urticaria	1
Total reactions	1125
Total reports	626

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[2])	Number of cases
Blood and lymphatic system disorders	Lymphadenopathy	7
	Palpitations	2
	Sinus tachycardia	1
Ear and labyrinth disorders	Ear pain	3
	Tinnitus	1
Eye disorders	Dry eye	1
	Excessive eye blinking	1
	Eye swelling	1
	Photophobia	1
	Vision blurred	4
	Visual impairment	1
Gastrointestinal disorders	Abdominal pain lower	1
	Abdominal pain upper	1
	Abnormal faeces	1
	Colitis ulcerative	1
	Diarrhoea	1
	Mouth ulceration	1
	Nausea	2
	Vomiting	2
General disorders and administration site conditions	Abasia	1
	Axillary pain	1
	Chest discomfort	1
	Chest pain	2
	Chills	3
	Fatigue	1
	Feeling abnormal	1
	Feeling cold	2
	Gait disturbance	1
	Influenza like illness	9
	Malaise	3
	Oedema peripheral	2

	Pain	3
	Peripheral coldness	5
	Pyrexia	1
	Swelling	1
Infections and infestations	Application site pustules	1
	Folliculitis	1
	Influenza	1
	Nasopharyngitis	1
	Pneumonia viral	1
	Streptococcal sepsis	1
	Urinary tract infection	2
	Viral infection	1
Injury, poisoning and procedural complications	Contusion	3
	Drug exposure during pregnancy	2
Investigations	Blood glucose increased	3
	Blood pressure increased	1
	Respiratory rate increased	1
	Weight decreased	2
Metabolism and nutrition disorders	Anorexia	1
	Decreased appetite	1
	Dehydration	1
	Diabetes mellitus inadequate control	1
	Diabetic ketoacidosis	1
	Hypoglycaemia	1
Musculoskeletal and connective tissue disorders	Back pain	1
	Flank pain	1
	Muscle twitching	1
	Muscular weakness	4
	Musculoskeletal chest pain	1
	Musculoskeletal stiffness	3
	Myalgia	1
	Neck pain	2
	Pain in extremity	10
Nervous system disorders	Complex regional pain syndrome	1
	Convulsion	4
	Dizziness	4
	Dysarthria	1
	Epilepsy	1
	Facial palsy	1
	Grand mal convulsion	1
	Guillain-barre syndrome	1
	Hemiparesis	1
	Hypoaesthesia	2

	Lethargy	1
	Loss of consciousness	2
	Migraine	4
	Optic neuritis	1
	Paraesthesia	3
	Sensory disturbance	1
	Sensory loss	1
	Somnolence	9
	Status epilepticus	1
	Syncope	4
	Tremor	3
	Unresponsive to stimuli	1
	Visual field defect	1
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	3
Psychiatric disorders	Confusional state	1
	Crying	2
	Eating disorder	1
	Emotional disorder	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
	Genital haemorrhage	1
	Menorrhagia	1
	Menstrual disorder	1
	Menstruation irregular	1
	Vaginal haemorrhage	1
	Vulval ulceration	1
Respiratory, thoracic and mediastinal disorders	Asthma	1
	Dyspnoea	5
	Epistaxis	2
	Haemoptysis	1
	Hypoventilation	1
	Nasal congestion	1
	Oropharyngeal blistering	1
	Oropharyngeal pain	4
	Rhinorrhoea	1
	Wheezing	2
Skin and subcutaneous tissue disorders	Acne	1
	Alopecia	2
	Blister	2
	Eczema	2
	Erythema	1
	Erythema multiforme	1
	Guttate psoriasis	1
	Hyperhidrosis	1

	Hypoaesthesia facial	1
	Rash	2
	Rash maculo-papular	1
	Rash vesicular	1
	Skin discolouration	3
	Skin exfoliation	1
	Skin lesion	1
	Urticaria	1
Vascular disorders	Flushing	1
	Haemorrhage	2
	Pallor	1
Total reactions		238
Total reports		153

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.