Safeguarding public health

Suspected Adverse Reaction Analysis

Human papillomavirus (HPV) vaccine (brand unspecified)

29 July 2010

This is the final routine report summarising the 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 between 14 April 2008 and 28 July 2010.

Since the start of the UK HPV immunisation programme in September 2008, MHRA has published these safety reports on a weekly basis. Now that the second school year of the HPV immunisation programme has come to a close, MHRA will cease production of weekly updates. Of course, as with all other vaccines used in the UK, the MHRA will continue to actively monitor the safety of HPV vaccine. However, from 30 July, updates on suspected adverse reaction reports will be provided on request only. These can be obtained by e-mailing **pharmacovigilance@mhra.gsi.gov.uk**.

Suspected adverse reaction 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, 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 such as faints).

[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

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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 at least 4 million doses across the UK since September 2008, the balance of risks and benefits of Cervarix remains positive

SUMMARY OF UK SAFETY EXPERIENCE

Total number of reports received: 258
Total number of suspected reactions: 737
Estimated number of doses of Cervarix administered across the UK: at least 4 million doses[3]

A. Injection-site reactions

Injection-site reactions including redness, pain and swelling are recognised[4] side-effects of HPV vaccines and are listed in the product information. These may occur at a frequency[5] 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	16
Oedema peripheral	9
Injection site swelling	6
Pain	6
Erythema	5
Injection site erythema	5
Musculoskeletal stiffness	4
Feeling hot	3
Injection site reaction	3
Hypoaesthesia	2
Injection site coldness	2
Injection site discolouration	2
Injection site mass	2
Injection site pain	2
Peripheral coldness	2
Pruritus	2
Sensory loss	2
Skin discolouration	2
Skin reaction	2
Tenderness	2
Hyperaesthesia	1
Hypokinesia	1
Injection site anaesthesia	1
Injection site haematoma	1

[3] Based on UK-wide vaccine uptake data up to the end of 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

Injection site haemorrhage	1
Injection site movement impairment	1
Injection site rash	1
Limb immobilisation	1
Local reaction	1
Local swelling	1
Lymphoedema	1
Mass	1
Mobility decreased	1
Muscle rigidity	1
Musculoskeletal pain	1
Paraesthesia	1
Rash	1
Sensation of heaviness	1
Urticaria	1
Total reactions	**98**
Total reports	**53**

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

Allergic reactions are a recognised[4] side-effect of HPV vaccines and are listed in the product information. These may occur at a frequency[5] 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	13
Urticaria	8
Dyspnoea	5
Eyelid oedema	4
Hypersensitivity	4
Dermatitis allergic	3
Erythema	3
Rash erythematous	3
Rash macular	3
Rash pruritic	3
Anaphylactic reaction	2
Blister	2
Dizziness	2
Heat rash	2
Lip swelling	2
Pharyngeal oedema	2
Pruritus	2
Rash generalised	2
Swollen tongue	2
Contusion	1

Dysphagia	1
Eczema	1
Fatigue	1
Feeling hot	1
Headache	1
Laryngeal oedema	1
Lethargy	1
Myalgia	1
Nausea	1
Oedema mouth	1
Paraesthesia oral	1
Pyrexia	1
Somnolence	1
Stridor	1
Swelling	1
Swelling face	1
Throat irritation	1
Throat tightness	1
Type IV hypersensitivity reaction	1
Urticaria pigmentosa	1
Vomiting	1
Total reactions	**89**
Total reports	**50**

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	27
Dizziness	15
Headache	9
Pallor	5
Vomiting	4
Dyspnoea	3
Nausea	3
Rash	3
Somnolence	3
Blood pressure increased	2
Heart rate increased	2
Hyperventilation	2
Malaise	2
Muscular weakness	2
Presyncope	2
Vision blurred	2

Abdominal discomfort	1
Abdominal pain	1
Asthenia	1
Back pain	1
Blindness transient	1
Body temperature decreased	1
Chills	1
Convulsion	1
Disturbance in attention	1
Dry mouth	1
Fatigue	1
Heart rate irregular	1
Hot flush	1
Hyperhidrosis	1
Hypoaesthesia	1
Migraine	1
Paraesthesia	1
Photophobia	1
Pruritus	1
Pyrexia	1
Sensory loss	1
Tremor	1
Urticaria	1
Visual impairment	1
Total reactions	**110**
Total reports	**46**

D. 'Other recognised' reactions

This section includes other events recognised[4] 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**
Headache	30
Nausea	28
Malaise	25
Pyrexia	24
Vomiting	16
Dizziness	15
Fatigue	12
Abdominal pain	8
Lethargy	6
Abdominal pain upper	5
Asthenia	4
Body temperature increased	4
Myalgia	4

Back pain	3
Decreased appetite	3
Diarrhoea	3
Somnolence	3
Dizziness postural	2
Influenza like illness	2
Limb discomfort	2
Musculoskeletal stiffness	2
Oropharyngeal pain	2
Pain	2
Abdominal pain lower	1
Arthralgia	1
Body temperature fluctuation	1
Cough	1
Feeling of body temperature change	1
Gastrointestinal disorder	1
Hot flush	1
Hypoaesthesia	1
Local reaction	1
Lymphadenopathy	1
Musculoskeletal discomfort	1
Neck pain	1
Pain in extremity	1
Respiratory tract infection	1
Total reactions	**219**
Total reports	**90**

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	3
	Hyperacusis	1
Endocrine disorders	Adrenocortical insufficiency acute	1
Eye disorders	Eye discharge	1
	Eye pain	1
	Photopsia	1
	Vision blurred	7
	Visual impairment	2
Gastrointestinal disorders	Abdominal discomfort	1
	Abdominal pain	6
	Abdominal pain upper	1

	Diarrhoea	1
	Gingival disorder	1
	Nausea	4
	Vomiting	1
General disorders and administration site conditions	Abasia	2
	Asthenia	1
	Chest discomfort	1
	Chest pain	1
	Chills	1
	Condition aggravated	1
	Discomfort	1
	Exercise tolerance decreased	1
	Fatigue	8
	Feeling abnormal	1
	Feeling cold	2
	Gait disturbance	2
	Influenza like illness	8
	Injection site injury	1
	Local swelling	1
	Malaise	2
	Oedema peripheral	1
	Pain	1
	Pyrexia	3
	Temperature intolerance	1
	Tenderness	1
	Thirst	1
Infections and infestations	Herpes zoster	1
	Infection	1
	Labyrinthitis	1
	Skin infection	1
	Upper respiratory tract infection	1
Injury, poisoning and procedural complications	Axillary nerve injury	1
Investigations	Body temperature increased	1
	Weight decreased	1
Metabolism and nutrition disorders	Decreased appetite	1
	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	2
	Pain in extremity	2
Nervous system disorders	Balance disorder	1
	Chorea	1
	Complex regional pain syndrome	2
	Convulsion	3
	Dizziness	12
	Dizziness postural	2
	Dysgeusia	1

	Dyskinesia	1
	Encephalitis	1
	Epilepsy	3
	Facial palsy	1
	Grand mal convulsion	2
	Guillain-barre syndrome	1
	Headache	11
	Hypoaesthesia	7
	Lethargy	4
	Loss of consciousness	2
	Migraine	1
	Neuritis	1
	Paraesthesia	6
	Sensory loss	1
	Somnolence	1
	Syncope	7
	Tremor	3
Psychiatric disorders	Confusional state	2
	Depression	1
	Dissociation	1
	Insomnia	1
Renal and urinary disorders	Urinary retention	1
Reproductive system and breast disorders	Amenorrhoea	2
	Menorrhagia	1
	Menstrual disorder	1
	Menstruation delayed	1
	Menstruation irregular	1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1
	Nasal congestion	1
	Oropharyngeal pain	1
	Wheezing	1
Skin and subcutaneous tissue disorders	Acne	1
	Alopecia	3
	Alopecia areata	1
	Dry skin	1
	Erythema	1
	Erythema multiforme	1
	Henoch-schonlein purpura	1
	Hyperhidrosis	1
	Hypoaesthesia facial	1
	Livedo reticularis	2
	Petechiae	1
	Photosensitivity reaction	2
	Purpura	2
	Rash	4
	Rash erythematous	1
	Skin burning sensation	1
	Skin disorder	1
	Urticaria	1
	Vitiligo	1
Vascular disorders	Pallor	2
	Peripheral coldness	3

Total reactions		**221**
Total reports		**86**