# Minutes of the

# Adverse Drug Reactions

# Advisory Committee

**311th meeting**

**24 October 2008**

## 5.2 United Kingdom

- Drug Safety Update. September 2008 (Vol 2/2)

Members noted in particular the article on *Introduction of human papilloma virus immunisation in the UK*. **The table describing the clinical features of anaphylaxis, as distinct from other allergic reactions, was noted in particular and Members suggested this table may usefully be included in a Bulletin article on allergic reactions to drugs in general, including to topical drugs (see item 7.1.1, below).**

[redacted]

### 10.1.1 Allergic reactions to HPV vaccine – cluster of reports

The reports associated with this item were due for review at the December meeting but were brought forward because reactions with HPV vaccine were currently under intensive surveillance by the Committee.

### Background

The NSW Department of Health had submitted 9 reports of allergic reactions to HPV vaccine, occurring over a period of 90 min in girls (4 aged 13 years, 2 aged 14, 3 aged 15) participating in a school-based immunisation clinic at a NSW school. On the day these events occurred, year 7, 8, 9 and 10 girls were scheduled to receive their 3rd dose of HPV vaccine; year 7 boys and girls were to receive their 2nd dose of hepatitis B vaccine on the same day. Prior to the events in the 9 girls, the vaccinations had proceeded without incident in all year 7 girls (who had received HPV vaccine from the same batch as that used for subsequent HPV vaccinations) and boys. The vaccination program was abandoned after all year 9 girls received their HPV vaccine. A tabulated summary of the reactions, provided by the Greater Western Area Health Service, is shown below:

| Case ADRAC No; Age | Time of Onset | Estimated time from vaccine to symptoms | ED admin. time | Time between onset to ED | Dis-charge time | Symptoms (compilation from multiple sources) | Medications |
|---|---|---|---|---|---|---|---|
| Case 1 244623 13yrs | 11.50am | 10 min | 1.10pm | 1.20 min | 6.50pm | Swelling & tightness right side of chest, itchy neck and shortness of breath | Adrenalin 12.26pm at school. Prednisone ED |
| Case 2 244641 13yrs | 12.00pm | 15 min | 1.50pm | 1.50 min | 5.45pm | Urticaria right side of neck, difficulty with breathing | Phenergan at 1:10pm by ambulance officer |
| Case 3 244635 13yrs | 12.00pm | 15 min | 1.55pm | 1.55 min | 5.30pm | Urticaria rash on right side of neck & on chest | Phenergan at 12:50pm by ambulance officer. Prednisone in ED |
| Case 4 244628 15yrs | 12.20pm | 20 min | 1.30pm | 1.10 min | 5.00pm | Urticaria Left shoulder & back | Phenergan at 1:38pm by ambulance officer |
| Case 5 244633 14yrs | 12.20pm | 5 min | 1.45pm | 1.25 min | 3.50pm | Urticaria right side of neck & sore throat | NIL |
| Case 6 244630 14yrs | 12.45pm | 26 min | 1.30pm | 45 min | 6.55pm | Itchiness & tightness in the throat | Adrenalin at 12:45pm and repeated at 1:00pm. Ventolin at 2:00 & 2:20pm. Prednisone in ED at 4:00pm |
| Case 7 244642 13yrs | 12.55pm | 15 min | 1.55pm | 1.00 hour | 5.30pm | Throat tightness, swollen tongue & difficulty breathing | Adrenalin at 12.55pm. Prednisone at 5.30pm and repeat dose. |
| Case 8 244643 15yrs | 1pm | 30 min | 2.30pm | 1.30 min | 3.50pm | Itchy in the throat & dizzy | NIL |
| Case 9 244629 15yrs | 1.20pm | 5 min | 2.00pm | 50 min | 7.10pm | Itchiness on right side of neck & upper arm | Panadol |

The NSW Health Department Population Health Division had provided all available documentation on the individual cases from the vaccination nurse, the ambulance officers and the Emergency Department. These were provided for review by ADRAC, along with the initial (Sep 22) and follow-up (Oct 9) reports on the incident from the Greater Western Area Health Service (GWAHS); the sponsor's preliminary (Sep 25) and updated (Oct 9) reports on the .. *Manufacturing Investigation related to GARDASIL® (Batch K3031*); and a publication that discussed the Brighton classification of anaphylaxis (Ruggeberg J. *et al*. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; 25: 5675–5684).

ADRAC was requested to review and provide comment on the 9 cases and the events surrounding these.

**ADRAC Discussion**

Members agreed that the conduct of the school's vaccination program was generally appropriately using standard protocols and follow-up procedures. The information suggested that the vaccine was administered into the "dominant limb" (presumably the right arm for most students), which was somewhat unusual. Reports of "skin rash at the injection site" may have been due to injection technique or may have resulted from local hypersensitivity reactions, but the notes were insufficiently detailed to allow definitive conclusions. The Committee was satisfied that the sponsor's investigations to date showed no evidence for concern over the quality of the vaccine used in these cases.

Member commented that the analyses of the events from the NSW Health Department was comprehensive, but the documentation of the individual cases (particularly from the vaccination nurse) was in some cases ambiguous and vague, and lacked sufficient detail to allow conclusive assessment of the clinical symptoms. A Member commented that the poor documentation by the vaccination nurses highlighted the need for a standard template to be developed that guided health professionals in describing more accurately and definitively any clinical signs, symptoms or events that occur after vaccination. For example, the template could include various criteria that should be met for describing "rash". There should also be a requirement for recording the exact time elapsing between the vaccine injection and the development of each sign. The template developed by the Canadian agency was cited as a good example that could be adapted for use in the HPV vaccination program [redacted] **undertook to provide this for the Committee's information.**

In general, the Committee considered it was likely that there was a large element of mass hysteria operating on the day these events occurred; enhancements to the program as suggested in the GWAHS report (particularly the recommendation to vaccinate away from view of other children) were likely to reduce the environment conducive to this type of response. It was agreed that cases 2, 3, 4, 5, 8 and 9 (see table above) did not warrant concern and were typical of minor urticarial or vasomotor reactions; the lack of respiratory symptoms in these cases was noted in particular. The remaining 3 cases (1, 6 and 7) which required administration of adrenaline were discussed in detail to decide whether the reactions were true anaphylaxis. The Committee agreed that additional information would have assisted the review of these cases, but it was noted that all information that was available was provided.

***Report 244623 (Case 1):***

The vaccination nurse's description of this reaction was ambiguous, particularly in relation to skin manifestations. It documented 'swelling (slight) [on right] side of chest, itchiness to [right] side at neck, short of breath, tightness, burning to [right] side of neck and into [right] ear.' There was no mention of rash being objectively observed. The ambulance officer report (which was prepared after

the patient had been given adrenaline by the vaccination nurse) describes 'blotchy skin', suggesting the reaction was more of a vasomotor rather than a hypersensitivity response. Skin reactions are not mentioned in the notes from the emergency department. Overall, ADRAC was unconvinced that rash had developed in this case; it was noted that the immunisation nurse's notes state: "rash on chest and tight breathing" recurred after 24 h, but this information was obtained from the patient by phone.

There were no respiratory symptoms of note in this case, apart from the subjective report of 'shortness of breath'.

ADRAC agreed case 244623 (NSW case No. 1) was not a case of anaphylaxis. There were no signs documented that objectively suggested anaphylaxis; any signs that were reported were those described by the patient. It was noted that the nurse had administered adrenaline.

***Report 244630 (Case 6)***

The vaccination nurse's notes on this case documented 'red rash on front of neck' and patient-reported symptoms of 'difficulty breathing and tight throat'; but the respiratory symptoms (monitored after the patient was given adrenaline) were objectively confirmed in the emergency department as 'bilateral wheeze'. Bilateral wheeze constituted a major respiratory component according to the Brighton case definition of anaphylaxis. The skin reaction appeared to be minor: the description of 'red rash on front of neck' could have been a vasomotor response, while the ambulance officer's report documented a subjective patient report of 'itch' rather than any objective description of a generalised rash. Members noted that the patient had a history of asthma and allergies (to penicillin).

On the basis of the presence of a major, objectively determined respiratory symptom (bilateral wheeze) and the minor skin reaction (localised rash or erythema), ADRAC agreed there was a Level 2 degree of certainty, according to Brighton Collaboration criteria, that report 244630 (NSW case 6) was a case of anaphylaxis.

***Report 244642 (Case 7)***

The vaccination nurse's notes for this case documented a minor respiratory component ('throat tightness and difficulty breathing') and a major skin component ('generalised urticaria; rash on throat, upper chest and both arms'). On this basis, ADRAC agreed there was a Level 2 degree of certainty, according to Brighton Collaboration criteria that report 244642 (NSW case 7) was a case of anaphylaxis.

The Committee had debated whether 'swollen tongue' should be given greater weight, but noted that respiratory signs (monitored after the patient had been given adrenaline) were not mentioned in the ambulance or emergency department notes, which tended to confirm that the respiratory component was minor.

**Summary and conclusion**

The Committee noted that the incident at the NSW school generated a level of concern that had been appropriately documented and investigated by NSW Health and the sponsor. ADRAC considered the incident did not represent a cluster of hypersensitivity reactions. Two students developed symptoms that would be classified as anaphylaxis with a Level 2 degree of certainty according to Brighton criteria; other reactions reported on the same day were minor skin reactions of various descriptions that can occur after vaccination in a school-based setting. There were no certain (Level 1) cases of anaphylaxis. The events tended to confirm the known association between HPV vaccine and hypersensitivity reactions, although the rate of this association is yet to be been determined.

The Committee agreed that the incident at the NSW school highlighted the need to develop a standard template that assisted the accurate and definitive recording of signs and symptoms of events occurring after immunisation.

**ADRAC recommended that a template be developed within the HPV immunisation program (possibly with assistance from ATAGI) to facilitate the clear, accurate, unambiguous and definitive recording of clinical signs and symptoms occurring after vaccination, for use within the immunisation program.**

### 10.1.2 Items for information

The following publications were noted for information:

- [redacted] *et al*. Anaphylaxis following quadrivalent human papillomavirus vaccination. *CMAJ* 2008; 179: 525-533. (see also commentary by Halsey, and La Page)
- [redacted] Monitoring vaccine safety: a critical component of every immunisation program. *MJA* 2008; 189: 243-244.
- [redacted] Human papillomavirus vaccination — Reasons for caution. *NEJM* 2008; 359: 861-862
- [redacted] *et al*, Mass psychogenic response to human papillomavirus vaccination. *MJA* 2008; 189: 261-262
- [redacted] *et al*. Pancreatitis following human papillomavirus vaccination. Letters to the Editor. *MJA* 2008; 189: 178
- [redacted] Rate of anaphylaxis after HPV vaccine higher than other vaccines, Australians report. Medscape Medical News 2008.

### 10.2 Vaccine reports

During the period from 22 July to 09 September 2008, 248 reports of vaccine adverse reactions were lodged. This represents about 20% of the reports lodged for the period. All case reports for vaccines received within the period were provided to the Committee.

***Reports of vaccines other than HPV vaccine***

181 of the vaccine reports describe reactions to vaccines other than single-injection HPV vaccine (4 of these describe reactions to HPV vaccine plus one other concomitant vaccine - hep B or DTPa).

73 of the reports were received from States, Territories or Local Government Councils, 93 were received from health professionals, 8 were from sponsors; and 7 were directly from consumers. Patient age was not stated in 4 reports; 142 reports related to children and 35 related to adults.

***HPV vaccine reports:***

67 of the vaccine reports described reactions to HPV vaccine when given as a single vaccine. The reports were received from NSW (26, including 3 from the Australian Vaccination Network), VIC (15), QLD (16, including 6 from the AME Line), SA (3), WA (2), ACT (1), Tas (1) NT (1), and from the sponsor with no State identified (2).

**Events**

The number of reports received in association with the majority of the vaccines is shown below:

| Vaccine | No. reports | Vaccine | No. reports |
|---|---|---|---|
| [redacted] | | | |
| | | Human papilloma virus | 68 |

***Other events***

None of the reports received within the period had been coded 'anaphylaxis'. A report of miscarriage in a female given HPV (244155) was reviewed at item 11 of this agenda, but the Committee agreed an association with the vaccine was unlikely. Summarised details of other specific reactions associated with vaccines are shown in the Tables, below.

[redacted]

| Seizures/convulsions (8 reports)<br>Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination | | | | | | |
|---|---|---|---|---|---|---|
| **Case Number** | **Sex** | **Outcome Description** | **Onset Time** | **Age** | **Reactions/Report description** | **Trade Name Description** |
| [redacted] | | | | | | |
| 244112 | F | Recovered | 0 | 21 | Tonic clonic seizure 1 minute after 2nd Gardasil injection. | Gardasil |
| [redacted] | | | | | | |

| Other serious neurological cases | | | | | | |
|---|---|---|---|---|---|---|
| **Case Number** | **Age** | **Sex** | **Onset Time** | **Outcome** | **Reactions** | **Trade Name Description** |
| [redacted] | | | | | | |
| 243264 | | F | 17 | Recovered | Multiple sclerosis<br>Paresis<br>Blindness | Gardasil |
| 243347 | 25 | F | 2 | Not yet recovered | Guillain-Barre syndrome<br>Pleurisy | Gardasil |
| [redacted] | | | | | | |
| 244364 | | FF | 26 | Recovered with sequelae | Optic neuritis<br>Migraine | Gardasil<br>NORDETTE NOS |

| Other serious neurological cases | | | | | | |
|---|---|---|---|---|---|---|
| 244371 | | F | 24 | Not yet recovered | Lethargy<br>Pyrexia<br>Mouth ulceration | Gardasil |

| Injection site swelling/extensive limb swelling (33 reports) | | | | | | |
|---|---|---|---|---|---|---|
| [redacted] | | | | | | |
| 244119 | F | Not yet recovered | 0 | Injection site swelling<br>Injection site discolouration | Gardasil | |
| [redacted] | | | | | | |

| Reports of rash, urticaria or pruritus (n = 53). Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination | | | | | | |
|---|---|---|---|---|---|---|
| **Case Number** | **Sex** | **Outcome** | **Onset Time** | **Age** | **Reaction** | **Trade Name Description** |
| [redacted] | | | | | | |
| 243091 | F | Recovered | 0 | 17 | Rash | Gardasil |
| 243092 | F | Recovered | 3 | 15 | Urticaria | Gardasil |
| 243095 | F | Recovered | 2 | 12 | Injection site rash<br>Headache<br>Nausea | Gardasil [redacted] |
| [redacted] | | | | | | |

| Reports of rash, urticaria or pruritus (n = 53). Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination | | | | | | |
|---|---|---|---|---|---|---|
| **Case Number** | **Sex** | **Outcome** | **Onset Time** | **Age** | **Reaction** | **Trade Name Description** |
| 243262 | F | Not yet recovered | 139 | 26 | Rash<br>Face oedema<br>Oedema peripheral<br>C-reactive protein increased | Gardasil |
| [redacted] | | | | | | |
| 243341 | F | Recovered | 0 | 25 | Rash<br>Chest discomfort<br>Dyspnoea<br>Syncope | Gardasil |
| [redacted] | | | | | | |
| 243545 | F | Recovered | 0 | 13 | Rash<br>Malaise<br>Injection site pain | Gardasil |
| [redacted] | | | | | | |
| 243630 | F | Recovered | 1 | 15 | Rash generalised<br>Swelling face<br>Pharyngeal oedema<br>Ocular hyperaemia | Gardasil |
| 243650 | F | Recovered<br>Recovered | 0 | 16 | Nausea<br>Pyrexia<br>Injection site pain<br>Urticaria | Gardasil |
| [redacted] | | | | | | |
| 243692 | F | Recovered | 2 | 14 | Rash | Gardasil |
| [redacted] | | | | | | |

| Reports of rash, urticaria or pruritus (n = 53). Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination | | | | | | |
|---|---|---|---|---|---|---|
| **Case Number** | **Sex** | **Outcome** | **Onset Time** | **Age** | **Reaction** | **Trade Name Description** |
| [redacted] | | | | | | |
| 243759 | F | Recovered | 12 | 13 | Oedema peripheral<br>Pruritus | Gardasil |
| [redacted] | | | | | | |
| 243938 | F | Not yet recovered | 14 | | Pruritus<br>Headache<br>Chest discomfort<br>Syncope<br>Purpura<br>Fatigue<br>Dizziness | Gardasil |
| 243943 | F | Not yet recovered | 2 | 14 | Pruritus Urticaria | Gardasil |
| 243946 | F | Not yet recovered | 23 | | Urticaria | Gardasil |
| 243957 | F | Unknown | 17 | | Urticaria | Gardasil |
| [redacted] | | | | | | |

| Reports of rash, urticaria or pruritus (n = 53). Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination | | | | | | |
|---|---|---|---|---|---|---|
| **Case Number** | **Sex** | **Outcome** | **Onset Time** | **Age** | **Reaction** | **Trade Name Description** |
| [redacted] | | | | | | |
| 244279 | F | Not yet recovered | 12 | | Rash erythematous Pruritus Feeling hot | Gardasil |
| [redacted] | | | | | | |

### 10.2.1 HPV Vaccine reports with further information or for re-review

The Committee often received reports for vaccines (or other medicines) that contain insufficient information to allow assessment. In these cases, ADRAC recommends that further information be sought from the reporter and staff from the OMSM attempt to obtain this following the Meeting. When further information is obtained for a specific case, the report is not re-presented to the Committee unless there is a particular reason for doing so. Given the recent focus on HPV vaccine, a list was provided, below, of reports for which additional information had been provided (either on request or unsolicited), together with a summary of the additional information:

| Report | Reaction | Additional information |
|---|---|---|
| 229154 | Pyrexia, nausea, neck stiffness, injection site paraesthesia, guttate psoriasis, sore throat | New info: 16 Days post vaccination, onset of rash. Intense pruritic, blanching and slightly raised. Initially urticaria but now scaly almost psoriatic with surrounding blanching/pallor. Assessment was guttae psoriasis likely triggered by vaccine. see attached photos of rash |
| 230606 | Epilepsy aggravated | Case now considered as aggravation of epilepsy (2 episodes of generalised seizure 8 days apart) in patient with preexisting absence seizures only but previously unmedicated. |
| 232885 | Bronchospasm, distress, nausea, dyspepsia, angioedema, urticaria, face oedema | Further information- reaction occurred 6.5 hours (not greater than 24hrs as stated before) after vaccination with third dose. The patient has a history of atopic disease. Skin test after reaction was negative to HPV vaccine. Possibly a case of anaphylaxis. |
| [redacted] | | |
| 234004 | Vaginal swelling, haematoma, blistering; fever, myalgia, tiredness | Further information related to lab data: Biopsy showed non specific inflammation. Other diagnostic tests were viral swab, full STD screen, blood culture, FBC and urinalysis which revealed negative results. |
| 234469 | Nausea, syncope, unresponsive, amnesia | The patient reports that for one week following dose she also experienced dysarthria (difficult to put sentences together and writing numbers backwards), lethargy, vomiting and diarrhoea. |
| 234537 | Faint, itch, rash | The reaction is now summarised as fainting episode 5 mins post first dose Gardasil, followed by a syncopal seizure, and within 15 minutes urticarial rash. Recovered by the next day. Patient had history of similar events, and needle phobia. Skin testing post reaction was negative for HPV, on rechallenge with dose 2, developed urticarial rash within a few hours only. |
| 234616 | Generalised rash, epigastric pain, fever, pancreatitis, | Further information only in regard to MJA literature article (provided) re pancreatitis post HPV. |
| 234883 | Vaginal ulceration | Patient is non-sexually active. |
| 234884 | Vaginal ulceration, fever, backache, rigour | Further information relates to lab data: on10 June 2007 herpes virus PCR I & II was done and virus was not detected. the following laboratory tests were done: varicella zoster + CMV PCR, vaginal swab microscopy culture and sensitivity, full blood count, urine electrolyte test, liver function test, human chorionic gonadotropin test and STD screen. All the tests had normal results. |
| 235452 | Rheumatoid arthritis aggravated | Additional lab data and information of concomitant medications |
| 236307 | Venous thrombosis | Subsequent tests on 12 Dec 2007 showed the patient's protein C to be low at 5 and confirmed that she had protein C deficiency and Factor V Leiden Mutation- alternative explanation for thrombosis |

| Report | Reaction | Additional information |
|---|---|---|
| 236891 | Shoulder stiffness, injection site swelling and paraesthesia (with Cervarix) | Medical history adenocarcinoma |
| 237063 | Lymphadenopathy, weakness, fatigue, headache, insomnia, lethargy, vomiting. | Further information was received from the physician. It was reported that lymphadenopathy resulted in a medical or surgical intervention. A biopsy of lymph node was performed. The results were unclear: ANCA was positive and CRP was 28 (units not provided). Additional information not expected. |

This was noted.

#### 10.2.1.1 Allergic reaction with HPV vaccine (report 240965: re-review)

Report 240965 was previously presented at the 309th (Jul 08) ADRAC Meeting. It described a 12 year old girl who, 6 days after her first dose of Gardasil, developed an urticarial rash on her arms, legs, back, chest, neck and face, facial swelling and chest tightness. She was treated with promethazine and recovered. ADRAC was requested to re-review this report and advise if it was a case of anaphylaxis.

Members noted the report documented the absence of respiratory signs ('no wheeze, no SOB'); it was agreed this was not a case of anaphylaxis and the coding should be completed in terms of the reported symptoms (such as acute facial swelling) only.

[redacted]

#### 10.3.1 Facial palsy and HPV vaccine

Report 243168 involved the development of facial palsy 1 day after Gardasil injection in a 13 year old female. She recovered completely at the time of reporting (about 2 months after vaccination).

Members noted this was the 5th report of facial palsy following HPV vaccine. It was anticipated this and the other cases would be reviewed by the Gardasil Expert Panel (see item 10.4, below).

### 10.3.2 Multiple sclerosis, paraesthesia and HPV vaccine

Report 243264 was received *via* the AMEL from the mother of the 17 year old female patient. One week after receiving Gardasil, the patient complained of numbness starting on her torso from under the arms and down, progressively increasing over 2 weeks to include legs and feet. She was unable to walk without assistance and was hospitalised for 3 days. An MRI of the brain and spine identified 3 lesions, for which she was treated with IV methotrexate. After discharge she complained of flickering in the right eye and over the next 10 days she progressively experienced worsening vision and "all she could see was grey". She was readmitted to hospital and underwent further lumbar, brain and spinal testing and methotrexate treatment. Her sight has returned to normal gradually, and it had taken up to a year for her to regain her strength.

Members commented on the aggressive treatment (methotrexate - an immunosuppressant) used in this case. Although a diagnosis of multiple sclerosis had been provisionally made, Members speculated that this may have been a case of neuromyelitis optica (Devic's disease) or some other monophasic, acute demyelination episode. It was noted that this case was being followed up with the treating neurologist and would be assessed in detail by the GEP.

### 10.3.3 Allergic reactions and HPV vaccine

Report 243341 describes a 25 year old female who fainted after her first dose of Gardasil. On the same day in the evening, she was hospitalised with a 'large rash, chest tightness, difficulty breathing'. She was not given adrenaline although the patient stated (to the reporting nurse) that the doctors were "close to giving it to her".

Members agreed there was insufficient information to allow this case to be classified according to Brighton criteria for anaphylaxis. It was not clear if a "large rash" was intended to convey generalised urticaria; and there was no objective description of a respiratory symptoms/s. It was suggested this report be coded in terms of reported symptoms only. A request should be made to obtain further information, including hospital notes on this case, to determine if re-coding is warranted.

### 10.3.4 Pleurisy and HPV vaccine

Report 243347 is a patient self-report to the sponsor. It describes a 25 year old female who received her first dose of Gardasil and 2 days later fainted and later experienced extreme fatigue, paralysis on the left side, serious difficulty with breathing and left lung pleurisy. She was hospitalised and her symptoms lasted about 1.5 months after vaccination.

In reporting this case to the sponsor, the patient had suggested that the HPV vaccine "triggered Guillain Barre Syndrome", although this diagnosis was not confirmed. ADRAC considered this case was more likely one of pleuritic chest pain with unclear pathogenesis. Members were doubtful that this was Guillain Barre Syndrome and suggested the possibility of a thromboembolic event, although there was no information in the report to confirm this.

**The Committee agreed additional information was required before this case (243347) could be fully assessed.**

### 10.3.5 Injection site cellulitis, acute renal failure, septicaemia and HPV vaccine

Report 243345 was submitted by the sponsor who had sourced the case from a local newspaper. It described a 23 year old female who received her 3rd dose of Gardasil. After vaccination, the patient's

arm became very tender and the next day the arm started to swell and was extremely red. The patient was admitted to hospital and was initially diagnosed with cellulitis at the injection site. She subsequently developed acute renal failure and septicaemia but responded to treatment with antibiotics.

Members commented that the renal failure was likely to have been associated with sepsis rather than with the vaccine; although the initial cellulitis was probably associated with the immunisation.

### 10.3.6 Neurological reactions and HPV vaccine

Report 243536 describes a 32 year old female who received her 2nd dose of Cervarix and 24 h later developed weakness in her left arm, hand and fingers, and sensory loss (numbness) in her left arm, face and leg. Two weeks later, only facial numbness was reported to be ongoing.

Members agreed an assessment was not possible on the basis of information contained in the report. This case had been reviewed by the GEP after receipt of further information.

### 10.3.7 Syncopal convulsions and HPV vaccine

Report 244112 describes a 21 year old female who experienced "tonic clonic seizure" 1 min following her 2nd dose of Gardasil. There were no sequelae and the girl had no relevant medical history, although the report states the girl previously experienced typical vasovagal presyncopal symptoms after her 1st Gardasil dose. Members suggested the "tonic clonic seizure" was most likely syncopal rather than neurological in origin and suggested the report be re-coded as 'syncopal convulsion'.

### 10.3.8 Optic neuritis and HPV vaccine

Report 244364 describes a 27 year old female who developed optic neuritis and migrainous headache some time within 3 weeks after her first dose of Gardasil. She underwent an MRI scan, was treated with prednisone and recovered fully by the time of reporting (about 2 months after immunisation).

Members anticipated that his report would be reviewed by the GEP in the context of similar reports received in association with HPV vaccine.

## 10.4 Report on the activities of the Gardasil Expert Panel

The Principal Medical Adviser, OMSM, advised that a Gardasil Expert Panel (GEP) had been recently established to re-review the safety and efficacy profile of HPV vaccine (Gardasil in particular) in view of information obtained since the vaccine was registered. The Panel would also review the HPV vaccination program and the current surveillance measures to determine if there are areas that require attention. The Panel comprised a number of vaccines experts and epidemiologists and was intended to complement rather than replace the role of the ADRAC in reviewing individual ADR reports with HPV vaccines. To date, the Panel had focussed on reviewing reports of neurological reactions with Gardasil and later will review reports of pancreatitis. The Principal Medical Adviser tabled summaries of the reports reviewed by the GEP and advised that each of these had been followed up to the fullest extent possible.

ADRAC noted that many of the reports of neurological reactions originated from NSW; Members speculated that other States and Territories may not be recognising the association and therefore the rate may be under-estimated.

**ADRAC re-iterated the recommendation from the 309th (Jul 08) ADRAC Meeting that existing networks (such as the Australian Paediatric Surveillance Unit and Australian neurologists' networks) be mobilised to assist in raising awareness of a possible association between HPV vaccine and neurological reactions.**

**Members also suggested that it was in the public's interest that information on this possible association be made available *via* the TGA website and other relevant sources of public information, as this would assist those considering whether the vaccine is appropriate for themselves or their children to make informed choices.**

Members noted details of individual case reports of pancreatitis with HPV vaccine. At this time, it was not clear if there was a true association with the vaccine but this was an issue the GEP hoped to resolve. Interestingly, a similar signal did not appear to be emerging overseas, although other countries had reported relatively high rates of abdominal pain and appendicitis.

ADRAC Members commented that the HPV vaccination program provided an ideal setting to collect comprehensive data that could later be used to perform epidemiological studies. Although the program was well underway, it would still be of value to establish structures within the program that provided for the collection of such data.

**ADRAC recommended the GEP consider appropriate means (such as HPV vaccine registers) to collect data from the HPV vaccination program that could later be used in epidemiological studies.**

[redacted]

[redacted]

### 11.2.4 HPV vaccine and premature labour

Report 244155

A 24 year old female who received her second dose of HPV vaccine (Gardasil) gave birth 6.5 months later to a premature baby (gestation age 28 week) that subsequently died postnatally (no details of cause of death). The female was given her second HPV dose 1 day after her last known menstrual period; she had received her first dose 2 months prior to that time. The reporter states there was "no other causes for the premature labour".

***Other relevant reports***

The Committee has previously reviewed 2 cases of miscarriage in females vaccinated against HPV (at the 308th (May 08) Meeting). In both cases, an association with the vaccine was considered unlikely.

**Use in Pregnancy statements from the Gardasil PI:**

Gardasil in Category B2 for use in pregnancy and the PI states *"….Thus, there is no evidence to suggest that administration of Gardasil adversely affects fertility, pregnancy or infant outcomes"*.

Members noted that clinical trials of HPV vaccine included a reasonable assessment of use in pregnancy and there is currently no evidence of untoward effects.

**Published information**

Information on human papilloma virus and the HPV vaccine from Reprotox to date suggests no known association between the vaccine and pregnancy outcomes.

**Conclusion:**

ADRAC agreed an association with HPV vaccine in case 244155 was unlikely.

### 11.2.5 Isotretinoin and cleft palate

Report 244166

A female taking isotretinoin after she became pregnant (no details of treatment duration) gave birth to a baby girl with a cleft palate.

Isotretinoin is contraindicated in pregnancy, with its teratogenic properties well described in the Roaccutane PI:

*"Use in pregnancy. (Category X)*
*Isotretinoin is a known human teratogen and should not, under any circumstances, be administered during pregnancy (see Contraindications).*
*Roaccutane should only be prescribed by doctors who are experienced in the use of systemic retinoids and understand the risk of teratogenicity……..."*

This is the 6th report to ADRAC of congenital malformations in women taking isotretinoin during pregnancy (a further 64 reports describe drug exposure in pregnancy). The other 5 reports describe multiple congenital abnormalities including cleft palate, deafness and heart disorder; ear malformation, movement disorder and developmental delay; premature labour, retroplacental haematoma, placental infarction and fetal death; and congenital musculoskeletal anomaly and limb malformation.

Patients prescribed oral isotretinoin are requested to sign forms agreeing to refrain from becoming pregnant during treatment with the drug. It is not known if the patient in case 244166 complied with this requirement.

An association with isotretinoin in case 244166 was considered probable; the reports contains too few details to allow allocation of 'certain' causality.

[redacted]

**14 Australian media**

A collection of newspaper clippings on the following subjects was noted for information:

[redacted]

- HPV vaccine

[redacted]