

**Minutes of the
Adverse Drug Reactions
Advisory Committee**

317th meeting

18 September 2009

<i>10.2.1.1</i>	<i>Neurological reactions following HPV vaccine.....</i>	<i>44</i>
-----------------	--	-----------

Report No Paper No.	Sex, age	Suspected drug/s	Other drugs	Medical History	Cause of death	Causality*	Discussion
252796 9.5.4	16, F	HPV vaccine	Not reported	Not reported	Ovarian cancer	More plausible alternative explanation (progression of pre-existing disease)	The onset between diagnosis and the vaccine is 2 months, death occurred within 5 months. There is insufficient information and given the short timeframe it is felt that there is no clear causal relationship.

A member commented that the collection of spontaneous reports is akin to passively doing nothing to monitor post-market safety. Prospective, structured, active surveillance using a systematic approach should be required for any mass vaccination program. In view of the puzzling neurological events reported in those who had received the HPV vaccine (eg, see 10.2.1.1, below), Members suggested it may be useful to extend the active surveillance of neurological disorders with H1N1 influenza vaccine to cover events with HPV vaccine – eg, through a self-controlled series analysis over a 6 week period.

10.1.2 Published papers

The following were noted for information:

- Slade B *et al.* Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine. *JAMA* August 2009; 302: 750-757.
- Human papillomavirus vaccine (GARDASIL). Advice from the Therapeutic Goods Administration. (Updated 19 August 2009)

10.2 Vaccine reports from the 316th (Jul 09) Meeting

The review of these reports was held over from the previous ADRAC Meeting. The following summary of the data, presented at the 316th Meeting, was again provided at the current Meeting.

During the period from 13 April to 1 June 2009, 279 reports of vaccine adverse reactions were lodged. This represents about 21% of the reports lodged for the period. All reports received within the period 13 April to 1 June 2009 were again provided for re-review.

Reports of vaccines other than HPV vaccine alone

251 of the vaccine reports describe reactions to vaccines other than single-injection HPV vaccine (including 14 where HPV vaccine was administered together with other vaccines, mainly Hep B, although influenza or varicella + Hep B vaccines were also given in some cases).

146 of the reports were received from States, Territories or Local Government Councils, 74 were from health professionals, 17 were from sponsors; and 13 were from the AMEL of a member of the public. 131 reports related to children, 115 related to adults and age was not stated in 4.

HPV vaccine reports:

28 of the vaccine reports described reactions to HPV vaccine when given as a single vaccine. These were received from VIC (10), NSW (6), QLD (4), SA (4), WA (1), ACT (1) or from an unidentified State *via* the sponsor (2).

Number of reports and events

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

Vaccine	No. reports	Vaccine	No. reports
		Human papilloma virus	42

Seizures/convulsions (12 reports)**Note: onset time (if stated on report) is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination**

Number Source	Sex	Age	Onset Time	Outcome	Trade Name Description	Reactions
250215 NSW	F			Recovered	Gardasil	Grand mal convulsion

250572 VIC	F	13		Recovered	Gardasil [REDACTED]	Convulsion, syncope
---------------	---	----	--	-----------	------------------------	---------------------

250694 QLD		15		Recovered	Gardasil	Grand mal convulsion
---------------	--	----	--	-----------	----------	----------------------

Other serious neurological cases (5 reports)

Number Source	Sex	Age	Onset Time	Outcome	Trade Name Description	Reactions
250188 QLD	F	19	5	Not yet recovered	Gardasil	Aphasia, meningitis, paralysis
250642 NSW	F	24	415 464 2	Not yet recovered	Gardasil	Acute disseminated encephalomyelitis
250708 Sponsor	F			Not yet recovered	Gardasil	Multiple sclerosis

251256 NSW	F	25		Recovered with sequelae	Gardasil	Ataxia, CNS lesion, cerebellar syndrome, demyelination, dystharia, ocular dysmetria, saccadic eye movement, vaccination complication
---------------	---	----	--	-------------------------	----------	--

10.2.1.1 Neurological reactions following HPV vaccine

Report 250097 (VIC)

A 12 year old female with no previous visual problems experienced headache and sudden onset of blurred vision and progressive visual loss, starting within half an hour of Gardasil injection. The headache resolved the same day but loss in visual acuity (confirmed objectively) worsened over several days before resolving spontaneously 7 days after immunisation. No underlying cause was established for the reaction, despite extensive neurological and ophthalmological investigations. The girl's clinical history included a large congenital arachnoid cyst in her posterior fossa but MRI

after the vaccine was unchanged from an MRI performed 4 months prior to vaccination. The reporter (paediatrician) raised the possibility that the reaction was an “emotional response”.

Members agreed this was a puzzling case and it would be interesting to determine what the final diagnosis was as the girl apparently remained under clinical investigation. It was unclear if there was an association with HPV vaccine, but this case was of interest in the context of the range of other neurological reactions reported in those vaccinated with HPV vaccine.

Report 250642 (NSW)

Two days after receiving her 3rd HPV vaccine, a 25 year old female developed pain in the right eye and severe bilateral papillitis, which was treated with methylprednisolone and steroids. Three months later, the female developed headaches and 1 month after that she developed tonic spasms in her left hand and had a generalised seizure. The reporter (consultant neurologist) considered this was a very curious presentation of bilateral papillitis followed by a meningoencephalitis; not typical of multiple sclerosis or Devic’s syndrome/neuromyelitis optica. He classified the reaction as a steroid-sensitive relapsing acute disseminated encephalomyelitis.

Report 250708 (sponsor – State not identified)

This was a very poorly-detailed report of a female (age not stated) who received HPV vaccine and some (unspecified) time later developed symptoms of multiple sclerosis requiring hospitalisation.

251256 (NSW)

A 26 year old female received her 2nd dose of HPV vaccine about 1 month before the following symptoms developed over a 2 week period: “severe gait ataxia, moderate dysarthria, ocular dysmetria, slowed saccades, and marked dysmetria and dysidiadochokinesis of the limbs, right more than left”. Findings were reported to be “consistent with cerebellar outflow tract lesion. No changes on MRI or CSF studies to indicate multiple sclerosis. [There was] no clear response to IV methylprednisolone.”

The patient was reported to be improving gradually but had significant ongoing disability at the time of reporting (about 7-8 months after the onset of symptoms), including persisting cerebellar ataxia and dysarthria.

Members considered this was also a puzzling case where an association with vaccination was unclear. The report included a statement that the case was reviewed by a neurologist who suggested the diagnosis of postvaccinial demyelination and who claimed that similar cases had been reported in the UK. Members noted that results of neurological investigations, if any, were not provided for case 251256. **It was suggested that further information should be requested for this case.**

A Member noted that the Gardasil Expert Panel had disbanded but it was not clear whether or how the recommendations of that Panel were being progressed. It was also unclear whether reports of neurological events would continue to receive the same level of scrutiny now that the GEP was no longer active. **A Member requested information to address these issues be provided to ADRAC at the next Meeting.**

10.3 Vaccine reports for the current (317th) Meeting

During the period from 2 June to 21 July 2009, 244 reports of vaccine adverse reactions were lodged. This represents about 13% of the reports lodged for the period. All reports received within the period covered by this Meeting were provided for review.

Reports of vaccines other than HPV vaccine alone

209 of the vaccine reports describe reactions to vaccines other than single-injection HPV vaccine (including 7 where HPV vaccine was administered together with other vaccines, mainly Hep B, although influenza, varicella or MMR were also given in some cases).

186 of the reports were received from States, Territories or Local Government Councils, 36 were from health professionals, 13 were from sponsors; and 9 were from a member of the public. 158 reports related to children, 86 related to adults.

HPV vaccine reports:

35 of the vaccine reports described reactions to HPV vaccine when given as a single vaccine. These were received from VIC (10), NSW (7), QLD (7), SA (5), NT (2), ACT (1) or from an unidentified State *via* the sponsor (3).

Number of reports and events

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

Vaccine	No. reports	Vaccine	No. reports
---------	-------------	---------	-------------

Human papilloma virus	42
-----------------------	----

Deaths or anaphylaxis

There was one report of death in association with vaccines, involving death due to ovarian cancer in a female immunised with HPV vaccine (see item 9.4.4). Members agreed this was unlikely to be a vaccine-associated death.

Three reports have been coded with the term ‘anaphylactic reaction’:

Other events

Summarised details of other specific reactions associated with vaccines are shown in the Tables, below.

Seizures/convulsions (9 reports)						
Note: onset time (if stated on report) is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination						
Number Source	Sex	Age	Onset Time	Outcome	Trade Name Description	Reactions
252031 NSW	F	15	15	Recovered	Gardasil	Convulsion, mydriasis
253016 NSW	F	14	14	Recovered	Gardasil	Tonic convulsion
253047 AMEL	F	27	27	Not yet recovered	Gardasil	Convulsion, injection site swelling
253785 Sponsor	F	18	28	Not yet recovered	Gardasil	Abdominal pain upper, chest discomfort, chills, convulsion, dyspnoea, headache, hypoventilation, insomnia, palpitations, syncope, vomiting

Other serious neurological cases (2 reports)

Number Source	Sex	Age	Onset Time	Outcome	Trade Name Description	Reactions
254214 VIC	F	22		Not yet recovered	Gardasil	Altered Source of consciousness, feeling abnormal, loss of consciousness, pseudoneurological symptom

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

- HPV vaccination program