

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

310th meeting

5 September 2008

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- Das A *et al.* Pancreatitis following human papillomavirus vaccination. *MJA* 2008; 189: 178.2

This was one of a series of papers that were intended to describe events occurring in patients receiving the HPV vaccine in Australia. A Member commented that the data so far suggested a coincidental association between HPV vaccine and pancreatitis. However, there was a danger that some readers could misconstrue the association as being causal. Nevertheless, it was important that practitioners were aware of the types of events occurring with this relatively new vaccine.

- ██████████ HPV vaccine deemed safe and effective, despite reports of adverse events. *Medscape Medical News* 2008

- ██████████ *et al.* The predicted impact of vaccination on human papillomavirus infections in Australia. *International Journal of Cancer* 2008; DOI: 10.1002/ijc.23633

This was noted for information.

Reports of vaccines other than HPV vaccine

243 of the vaccine reports describe reactions to vaccines other than single-injection HPV vaccine; 13 of these describe reactions to HPV vaccine plus at least one other (mainly hepatitis B) concomitant vaccine.

200 of the reports were received from States, Territories or Local Government Councils, 29 were received from health professionals, 10 were from sponsors; 3 were from the AMEL, and 1 was from the Red Cross. Patient age was not stated in 3 reports; 171 reports related to children and 69 related to adults.

HPV vaccine reports:

91 of the vaccine reports described reactions to HPV vaccine when given as a single vaccine. The reports were received from NSW (34), VIC (26), QLD (12), SA (12), WA (1), ACT (2), NT (2), and from the sponsor with no State identified (2). Members noted that the number of reports for HPV vaccine was declining relative to the total number of reports for any vaccine.

All vaccines

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

Human papilloma virus (Gardasil)	91
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Seizures/convulsions (9 reports)

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	Trade Name Description
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242746	F	Recovered	0	13	Syncope, pallor, partial seizures	Gardasil
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Other serious neurological cases (21) (cases marked * were reviewed as a matter of priority at the 309 th ADRAC Meeting)						
Case Number	Sex	Outcome	Onset Time	Age	Reaction	Trade Name Description

242524	F	Not yet recovered	0	25	Injection site pain Paraesthesia, Pain in extremity	Gardasil
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242769	F	Not yet recovered	0	24	Injection site rash Injection site pain Paraesthesia, Insomnia Dizziness, Pyrexia Pain, Back pain, Dizziness, Myalgia	Gardasil
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242785*	F	Unknown	177 118	16	Headache Paraesthesia Central nervous system lesion	Gardasil
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242789*	F	Unknown	125 6	16	Asthenia Monoparesis Diplopia, Nausea Vomiting, Hypoaesthesia facial Myelitis transverse	Gardasil
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242793*	F	Unknown	143, 101, 3	16	Athetosis Asthenia, central nervous system inflammation	Gardasil
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242796*	F	Unknown	103	25	Multiple sclerosis Lethargy Hemiparesis	Gardasil
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242812	F	Recovered	0	14	Paraesthesia Dyspnoea Dizziness Pyrexia Nausea Headache	Human Papillomavirus Recombinant Vaccine NOS
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242877	F	Not yet recovered	5	13	Headache Malaise Dysarthria Ataxia Somnolence Mental impairment	Gardasil
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Other serious neurological cases (21)

(cases marked * were reviewed as a matter of priority at the 309th ADRAC Meeting)

Case Number	Sex	Outcome	Onset Time	Age	Reaction	Trade Name Description
242997	F	Not yet recovered		23	Hepatic failure Renal failure acute Metabolic encephalopathy	Human Papillomavirus Recombinant Vaccine
243038	F	Recovered	32, 93	21	Leukoencephalomyelitis	Gardasil
243040	F	Not yet recovered	0	26	Headache Vomiting Encephalitis	Gardasil
243055	F	Unknown		27	Personality change Aggression Syncope Nystagmus	Gardasil

Extensive limb swelling (62 reports)

***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
241762	F	Recovered	1	24	Injection site swelling Injection site reaction	Gardasil

Extensive limb swelling (62 reports)

***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
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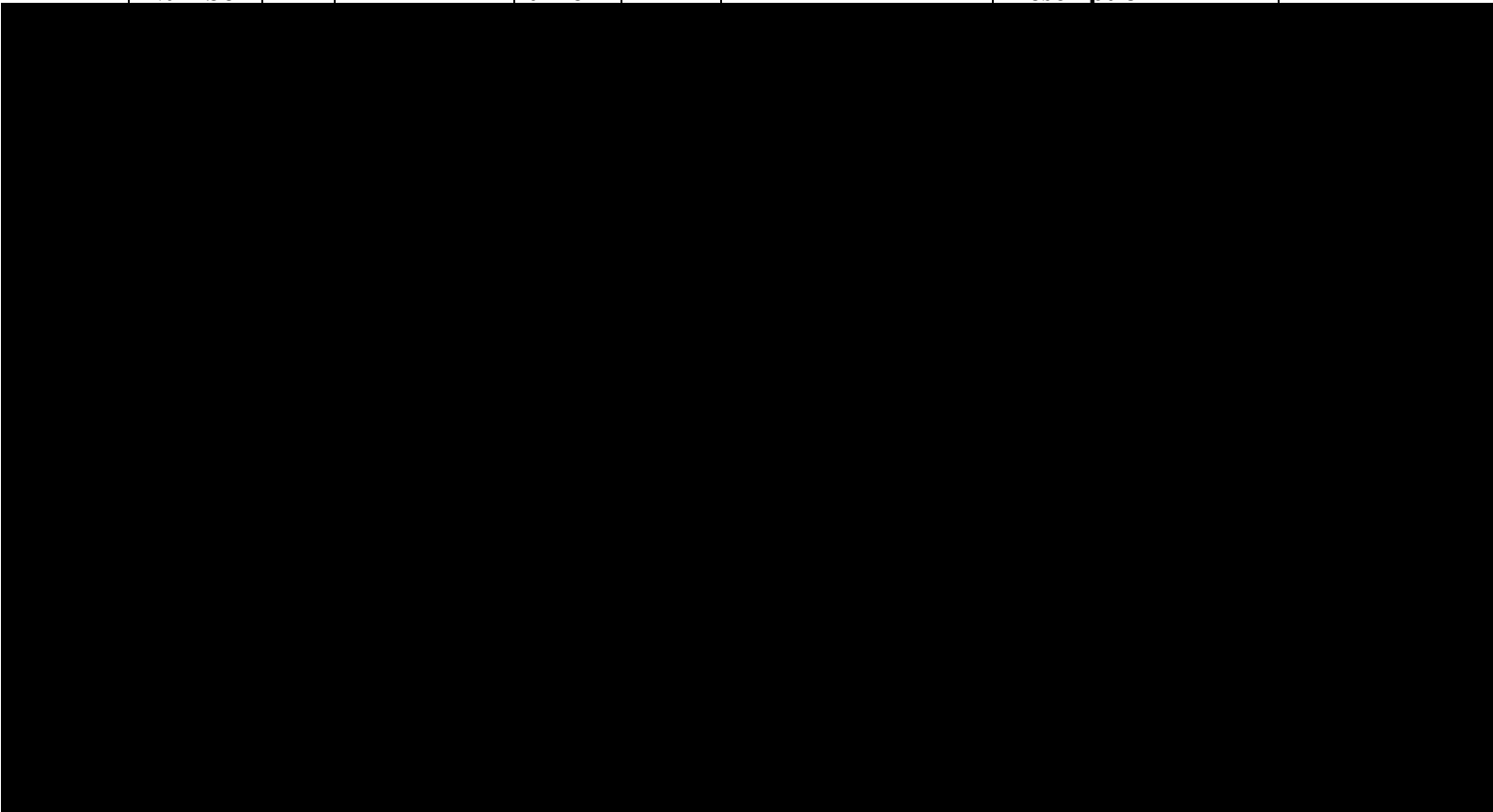
242507	F	Recovered	2	12	Injection site swelling	Gardasil HEPATITIS B VACCINE
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242526	F	Recovered	0	22	Injection site reaction Injection site swelling Injection site pain Pain in extremity Injected limb mobility decreased	Gardasil
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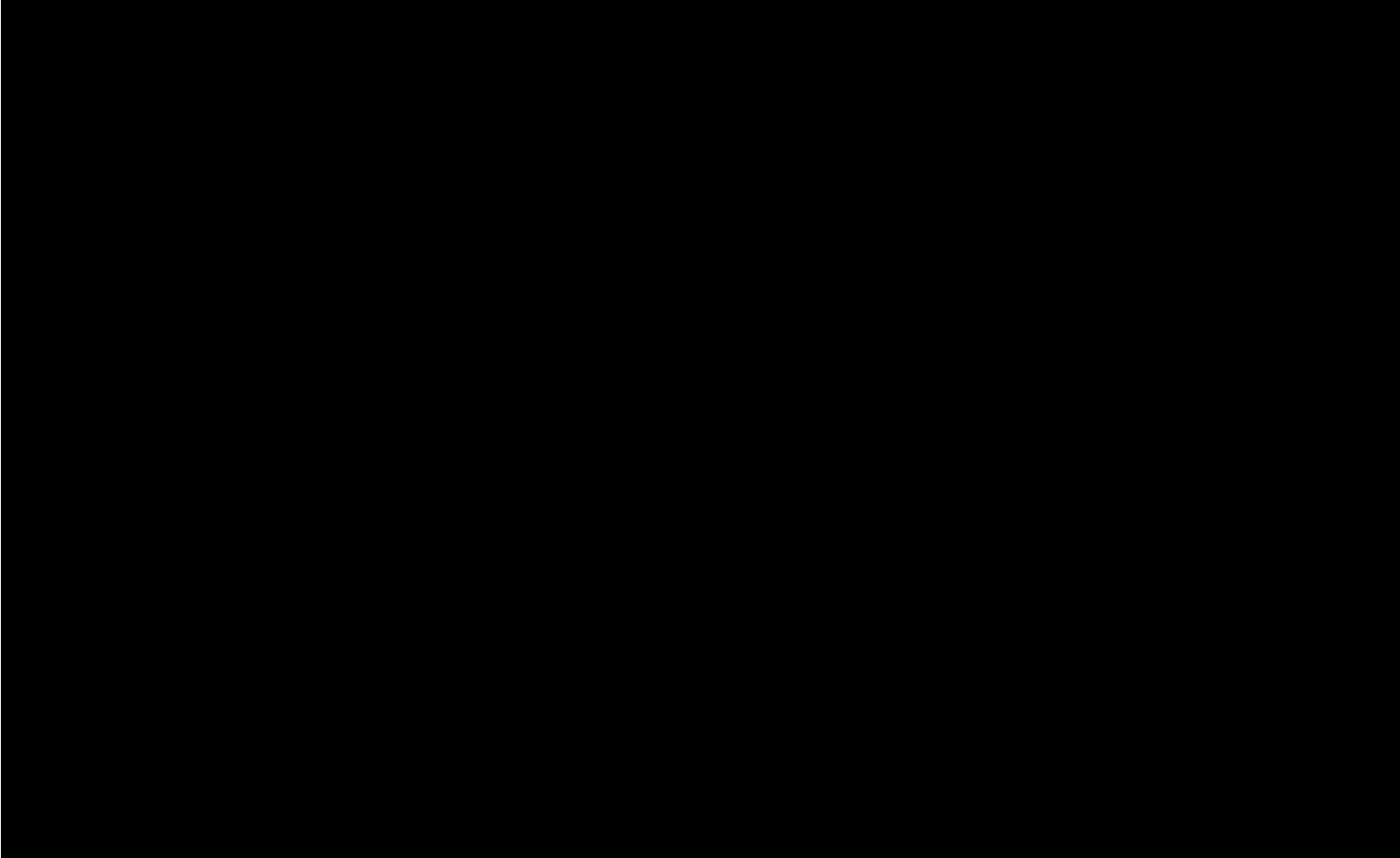
Extensive limb swelling (62 reports)

***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
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242834	F	Recovered	3	15	Injection site swelling	Gardasil
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Reports of rash, urticaria or pruritus (n = 91). Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination					
Case Number	Patient Age	Patient Sex	Outcome Description	Trade Name Description	Min Onset Time
241428	12	F	Recovered	Gardasil	0
241430	13	F	Recovered	Gardasil	1
241438	15	F	Recovered	Gardasil	0
241442	16	F	Recovered	Gardasil	0
241464	12	F	Recovered	Gardasil	0
241484	15	F	Not yet recovered	Gardasil	0
241493	23	F	Not yet recovered	Gardasil	

Reports of rash, urticaria or pruritus (n = 91). Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination

Case Number	Patient Age	Patient Sex	Outcome Description	Trade Name Description	Min Onset Time
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241500	12	F	Unknown	Gardasil	4
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241671	16	F	Recovered	Gardasil	2
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241737	15	F	Recovered	Gardasil	0
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241761	12	F	Unknown	Gardasil	0
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241817	23	F	Recovered	Gardasil	2
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241826	15	F	Recovered	Gardasil	2
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241850	12	F	Not yet recovered	Gardasil	2
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241853	11	F	Unknown	Gardasil	3
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242060	15	F	Recovered	Gardasil	1
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242205	15	F	Recovered	Gardasil	
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Reports of rash, urticaria or pruritus (n = 91). Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination

Case Number	Patient Age	Patient Sex	Outcome Description	Trade Name Description	Min Onset Time
242275	14	F	Recovered	Gardasil	0
242277	13	F	Recovered	Gardasil	1
242281	14	F	Recovered	Gardasil	2
242303	13	F	Recovered	Gardasil	0

242332	26	F	Recovered	Gardasil	
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242370	14	F	Not yet recovered	Gardasil	4
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242459	13	F	Unknown	Gardasil	0
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242473	12	F	Not yet recovered	Gardasil	0
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242570	16	F	Recovered	Gardasil	1
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Reports of rash, urticaria or pruritus (n = 91). Note: onset time is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination

Case Number	Patient Age	Patient Sex	Outcome Description	Trade Name Description	Min Onset Time
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242753	12	F	Not yet recovered	Gardasil	2
242754	14	F	Recovered	Gardasil	0

242759	26	F	Recovered	Gardasil	0
242769	24	F	Not yet recovered	Gardasil	0
242823	12	F	Recovered	Gardasil	0

243003	24	F	Not yet recovered	Gardasil	7-14
243005	12	F	Not yet recovered	Gardasil	5

10.3.1 Neurological events and HPV vaccine

A Member drew attention to the diverse range of neurological events that had been reported in association with HPV vaccine in the current period:

Report	Reaction description
242785	2 days post vaccination with 3rd Gardasil dose, 17 y.o patient developed headache then 2 days later developed spinal sensory syndrome and paraesthesia. She was referred to a neurologist who identified particularly aggressive multiple lesions. Four years prior to event the patient described vague episode of paraesthesia.
242793	After 1st Gardasil dose, the patient (16 y.o girl) experienced dizziness. After her 2nd dose, she had headaches and was concerned about memory impairment. A few days after the 3rd dose, the patient got up during the night and lost control of her legs and collapsed. The next morning she had recovered. Approximately 3 weeks after 3rd dose she developed right hand weakness and was referred to a neurologist who identified multifocal CNS inflammatory disorder, presented with pseudoathetosis. She recovered with treatment over 3 months.
242789	8 days after her 3 rd Gardasil dose, a 17 year old girl developed left leg weakness, monoparesis, nausea, vomiting, diplopia, and facial numbness.
242796	14-16 days after her 2nd Gardasil vaccination a 26 year old female experienced general lethargy and weakness in limbs (right sided hemiparesis), and ?encephalopathy (neurologist later diagnosed MS by MRI)
243038	Acute disseminated encephalomyelitis (ADEM), rapid onset of personality change, headache, generalised seizure and altered conscious state in a 22 year old (about 1 month after her 2 nd Gardasil dose).
243040	At night after receiving her first Gardasil dose, a 26 year old female developed a headache with became severe and was associated with vomiting. Symptoms persisted and she saw her GP a week later who thought the presentation was consistent with a diagnosis of viral encephalitis (although the basis for this diagnosis is not stated).

It was noted that some of the above cases were reviewed as a priority at the 309th ADRAC Meeting. However, the purpose of highlighting these and the additional cases was to illustrate the diverse nature of the neurological reactions that are being reported with HPV vaccine. Some of these have been confirmed by objective diagnostic criteria while the basis of the diagnosis for others is unclear and/or dubious. This makes it difficult to establish whether there is a causal relationship between HPV vaccine and any specific form/s of neurological reactions; however, it was important that this question be addressed and resolved promptly. The Member suggested case ascertainment was particularly important in this situation: each case should be followed-up and investigated to the fullest extent possible so that true neurological reactions are identified and distinguished from conversion-type disorders and from reactions that have been made on unsubstantiated grounds. This would assist in providing a greater understanding of the adverse events profile of HPV vaccine in general and in neurological terms.

10.3.4 Urticarial rash with HPV vaccine

Report 243003 described the development of extensive hives over the entire body of a 24 year old female 7-14 days on each occasion after she was given her 1st, 2nd and 3rd doses of Gardasil: the rash lasted for about 2 months on each occasion and a link with the vaccine was not made until after the 3rd dose. Allergy testing did not prove informative and the patient stopped responding to antihistamines. This case was notable for the consistent, double re-challenge pattern. The photographs accompanying this report showed an unusual, symmetrical pattern that was punctuated by vasculitic-like lesions at (presumably) the biopsy sites.

10.3.5 Allergic symptoms with HPV vaccine

Report 241715 described difficulty breathing, headache, nausea, pallor, angioedema and chest tightness, 30-40 minutes after a 14 year old female was given her second dose of Gardasil. The symptoms were stated to have lasted 1 h but she was treated at the scene with adrenaline before being transferred to an Emergency unit.

A Member familiar with this case advised it was not yet certain if this was an anaphylactic reaction to Gardasil. Although the reaction did include respiratory, dermal and gastrointestinal symptoms, the onset time is later than expected for anaphylaxis. Investigations were currently on-going and advice of the outcome would be provided in due course.

10.3.6 Report with HPV vaccine requiring follow-up

Report 242997 described a 24 year old female who was found by her parents (1 day after they last saw her) to be “frothing at the mouth and blue”. The girl was taken to hospital where she experienced “continuing tonic-clonic seizure activity” and subsequently developed hepatic failure, metabolic encephalopathy and renal failure.

HPV vaccine (brand not specified) was listed in the report as a suspected drug but further information from one of the treating doctors indicated no record of this vaccine being administered. There was also some suggestion that the patient had taken valproate at some stage but this was discontinued.

A Member was doubtful that this was a vaccine-associated event and suggested further review of this case await further information that was being currently being sought.

14 Australian media

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

- HPV vaccine – reactions and monitoring