

**Minutes of the
Adverse Drug Reactions
Advisory Committee
307th meeting
11 April 2008**

10.1.2 Gardasil and vulvovaginal reactions27

10.2.2 HPV vaccine reports55

10 Vaccines

10.1 Issues and publications

The following papers were noted for information:

10.1.2 Gardasil and vulvovaginal reactions

At a previous meeting, members requested a review of reports of vulvovaginal reactions following Gardasil immunisation.

Reports to TGA

To 27 February 2008, TGA has received 749 reports of reactions associated with Gardasil, including 12 reports of vulvovaginal reactions. Three of these describe candidiasis (2 reports) or PV bleeding (1 report), and will not be discussed further. The 9 others are tabulated and described below. Most of the reports do not have any further significant information than that presented below; therefore, original reports were presented for only three of the cases – 228983, 235450, and 236132.

Report	age	Reactions	time to onset (days)	recovery?*	source
228983	12	rash; vulvovaginal pruritus	0	No	ACT Health
234004	16	vaginal mucosal blistering	0	No	NSW Health

234508	17	genital ulceration	14	Yes	VIC GP
234883	?	vaginal ulceration	?	Unstated	NSW GP
234884	?	vaginal ulceration	?	Unstated	NSW GP
235391	16	vaginal inflammation, blistering	2	Yes	NSW Health
235450	25	vulval inflammation	1	No	QLD Health
235631	17	vaginal blistering rash	1	No	NSW Health
236132	23	vulvovaginal papilloma	0	No	NSW GP

*at time of reporting

228983: A 12 year old with a past history of eczema developed an itchy rash on her chest and back, and vaginal itch, several hours after immunisation. 3-4 days later, the rash was fading but still present. No treatment was given.

234004 : A 16 year old, not sexually active, developed vaginal blistering the evening after vaccination; biopsy and serology were described as “NAD; negative for virus”.

234508: A 17 year old, with one sexual partner, developed ulceration on the labia and perineum two weeks after immunisation. 2x HSV PCR swabs were negative, and serology was negative at 6 weeks.

234883: This report received from an email discussion group describes a non sexually active female who developed vaginal ulceration a few days after immunisation and required hospitalisation.

234884: This report received from an email discussion group describes a non sexually active female who developed vaginal ulceration a few days after immunisation and required hospitalisation.

235391: A 16 year old, not sexually active, developed vaginal inflammation and blistering 2 days after immunisation; the lesions resolved 7 days later.

235450: A 25 year old developed vulval inflammation the day after immunisation; the rash was worsening 6 days later, requiring treatment with topical steroids.

235631: A 17 year old developed blistery rash extending “from waist to knees” with accompanying vaginal irritation, the day after immunisation. The rash subsided and then flared again, and the patient was referred to a dermatologist.

236132: A 23 year old developed vulvovaginal warts after immunisation (the report states onset of reaction on the day of immunisation).

Other information

The PSUR for Gardasil covering the period 1 June 2007 to 30 Nov 2007 contained the following:

Australia: 6 reports: 2 serious reports of vaginal ulceration; 3 nonserious reports of vaginal ulceration; 1 report of vulvovaginal pruritus and rash.

USA: 4 reports: vaginal ulceration, pain, and herpesvirus infection; “vaginal lesion”; genital rash; vulvovaginal pruritus and rash.

The pre-market evaluator reports that this kind of event was not mentioned as a serious adverse event in clinical trials up to the January 2006 cut-off date.

It should be noted that the mechanism of action of Gardasil is through the induction of antipapillomavirus antibodies. Gardasil contains HPV 6,11,16,18 L1 virus-like particles (VLPs). Each VLP is composed of a unique recombinant L1 major capsid protein for the respective HPV type. Because the VLPs contain no viral DNA, they cannot infect cells or reproduce.

Summary

TGA has received 8 reports of vaginal rash/ulceration/blistering, and one report of vulvovaginal papilloma, following immunisation with Gardasil. Some of these reports may be consistent with an allergic-type reaction. These reports should be considered in the context of the number of Gardasil doses so far administered, which was estimated to be on the order of 2 million doses at the end of 2007. Expert opinion (from [REDACTED] has been sought on these specific case reports, and on the likely background incidence of vulvovaginal lesions in this population, but a response had not been received at the time of this meeting.

The ADRAC vaccine expert referred to the nine reports that had been tabulated and again commented that this was an unusual adverse event and it would be of importance to establish the occurrence of vulval/vaginal ulceration as a background in adolescent girls. Expert opinion from an adolescent gynaecologist had previously been sought however the name of a second gynaecologist was provided for advice on this matter. It was also mentioned that Epstein-Barr virus infection, which is prevalent in adolescents can manifest with symptoms of vulval/vaginal ulceration and that this association would need to be discussed with the specialist.

A member commented that the average onset time was approximately 24 hours post vaccination, and commented that this time frame is short for a typical autoimmune response. It was also noted that this reaction may be a flare-up of an existing HPV infection. The vaccine does not contain a live virus so there is no risk of cross-infectivity. One of the patients in the reports had undergone a lesion biopsy and members indicated that it would be useful to follow up any laboratory results. ADRAC will continue to monitor the issue and evaluate the advice and comments that either adolescent gynaecologist is able to provide.

10.2 Vaccine reports

During the period from 5 January 2008 to 23 February 2008, 244 reports of vaccine adverse reactions were lodged. This represents about 18% of the reports lodged for the period.

There were 41 reports describing extensive limb swelling related to non- HPV vaccines. There were NIL reports describing extensive limb swelling related to HPV vaccine.

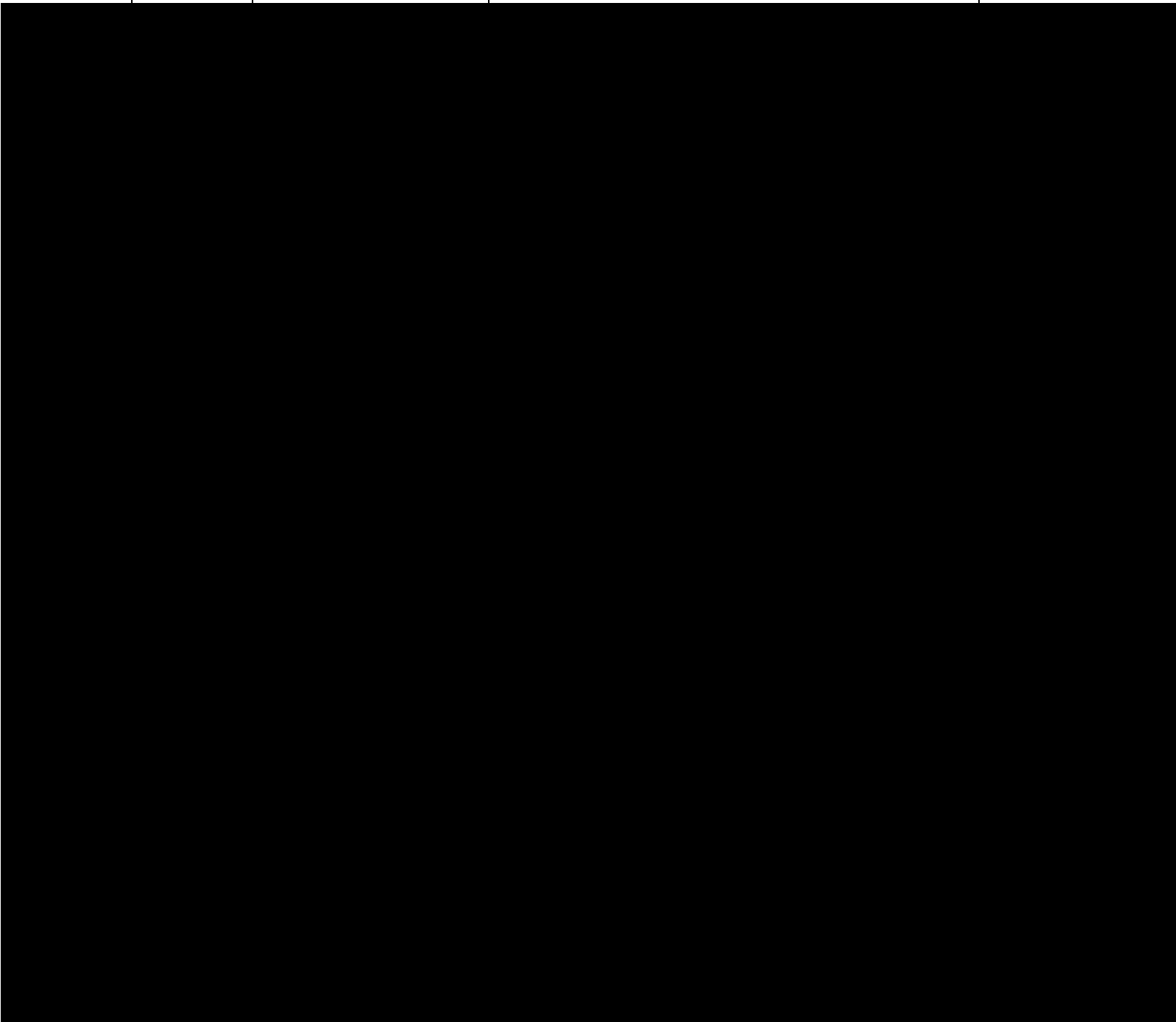
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page 31

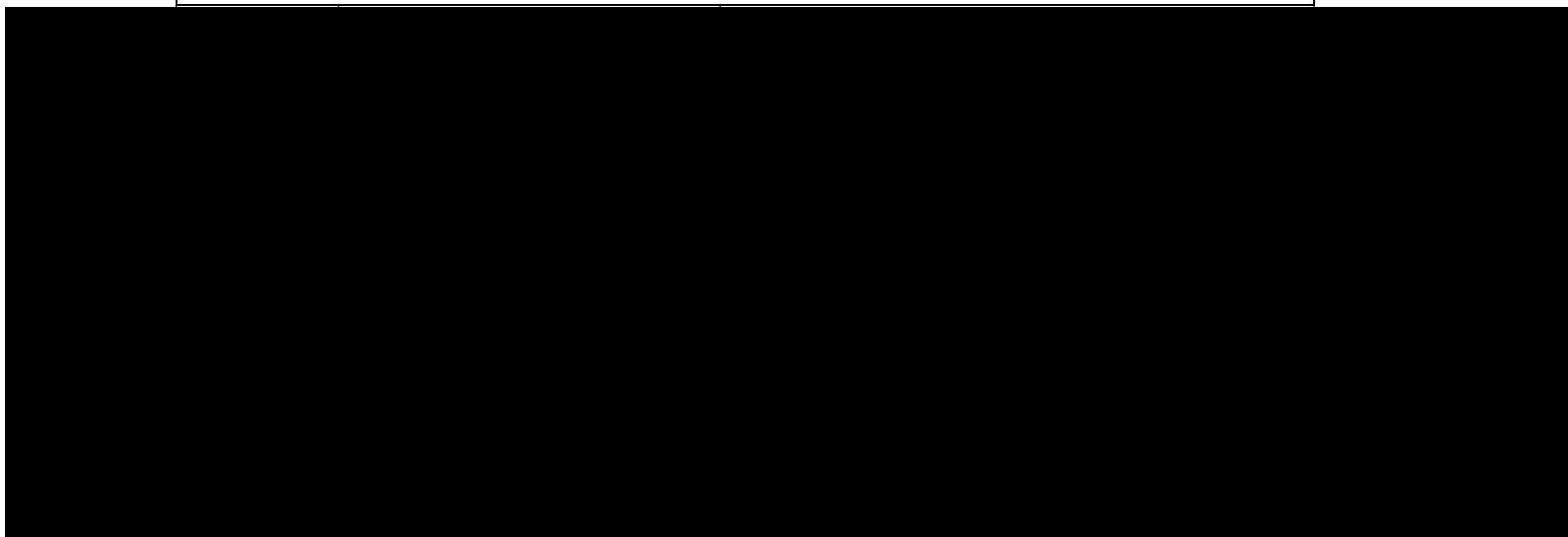
Seizures/convulsions (6 reports)

	V a c c i n e / s	Details
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<i>Minutes of the 307th (Apr 08) ADRAC Meeting</i>	H P V	27 y.o experienced seizures within a few hours of dosing and was hospitalised. No prior history of seizure. <i>page 32</i>
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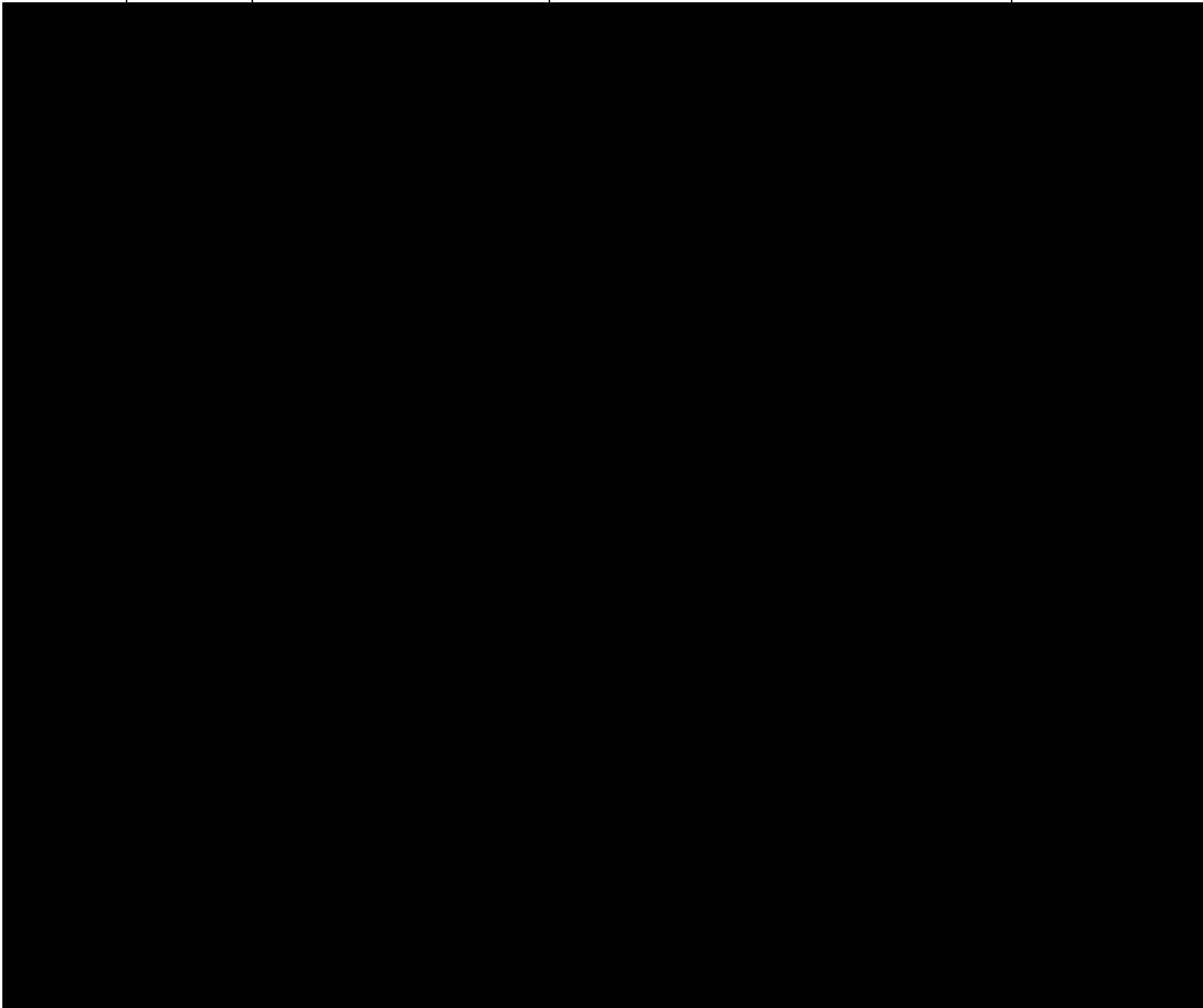
**GBS (1 report) and other serious reactions in SOC
'nervous system disorder'
(8 reports)***



		3 r d d o s e H P V	16 y.o initially had pain in the whole of left arm, and then 3 days later intermittent left arm paralysis and paraesthesia. Later presented with left facial, arm and leg hemiparesis. Recovered
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GBS (1 report) and other serious reactions in SOC 'nervous system disorder' (8 reports)*		
	s e H P V	walking, myalgia, fatigue. Not yet recovered



	H P V	16 y.o the neurologist diagnosed multiple sclerosis, with
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GBS (1 report) and other serious reactions in SOC 'nervous system disorder' (8 reports)*		
		the episode of right-sided numbness being the first attack and optic neuritis the second
	1 s t d o s e H P V	21 y.o female developed right sided facial paralysis one day after dose. Recovered.

Note: 89 vaccine reports include a term included in the system organ class 'Nervous system disorders'

Rash within 24 h (18 reports) Note: 38 reports in this period included 'rash', pruritus' or urticaria' as a reaction term . The reports tabulated are those that indicated or suggested onset time within 24 h.		
	V	Details

Rash within 24 h (18 reports)

Note: 38 reports in this period included 'rash', pruritus' or urticaria' as a reaction term . The reports tabulated are those that indicated or suggested onset time within 24 h.

	a c c i n e / s	
	H P V	Patient developed a rash and hives on her face which worsened on her face.
	H P V	Generalised urticaria and itchiness.

	H P V	Developed rash on abdomen, chest and neck.
	H P V	Swollen arm and rash around injection site. Rash spread to body.
	H P	Itchy rash on opposing arm, rash progressed

Rash within 24 h (18 reports)

Note: 38 reports in this period included 'rash', pruritus' or urticaria' as a reaction term . The reports tabulated are those that indicated or suggested onset time within 24 h.

	V	to lower legs and was itchy. No respiratory involvement, otherwise well.
	H P V	15 hours post vaccination developed a maculo-papular rash on limbs and torso, resolved in 24 hours.

10.2.2 HPV vaccine reports

The following HPV vaccine reports were noted:

Report number	Comments
237063	An unusual and interesting reaction
237100	Patient experienced pain in lower limbs and recently upper limbs following second dose of HPV vaccine. Suggestive of a neuropathic process, but could be functional disorder perhaps. Members asked for the case to be kept open and to consider writing to the reporting neurologist to consider testing for small fibre neuropathy if that had not already been excluded. Members agreed that from the scans and the Doctor's assessment the reaction did not appear to be due to a central process.
237678	Elevated LFT more likely associated with virus or oral contraceptive than vaccine.
237774	Blistering rash an interesting reaction.
237812	MS and optic neuritis unlikely due to vaccine.
237957	Requires re-coding. Reaction described is not 'brachial neuritis'

ADRAC discussion

The members were interested to find out about the newly created project officer position in ADRU. This position involves exploring a coordinated approach to vaccine safety monitoring within TGA with external stakeholders. ADRAC commended this new approach to vaccine safety monitoring.

A member commented that there is still a lot of misinformation relating to HPV vaccine in the public domain and it is worthwhile writing a Bulletin article about HPV vaccine. Some individuals agreed that it was the best to keep a single source of up to date information regarding the vaccine on the TGA website, however others believed that an additional source such as the Bulletin would provide better dissemination of information to health care professionals.