

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

308th meeting

30 May 2008

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HPV vaccine

8 (of total 23) convulsion; 1 (of total 4) grand mal convulsion; 4 (of total 17) unresponsive to stimuli

See item 10 of agenda

- Morbidity and Mortality Weekly Report, May 2, 2008; 57 (17).

The article on *Syncope After Vaccination — United States, January 2005–July 2007* was noted in particular. Members considered that the increase in post-vaccination syncope since 2005 in the US was most likely associated with the introduction of HPV vaccine, which is known to be a relatively painful vaccine. The context in which it is administered (ie, in public, school-based settings) almost certainly also contributes to the increased vasovagal reactions to HPV vaccine relative to other vaccines. Members noted the paper's recommendation to adhere to the 15 minute post-vaccination monitoring period in order to prevent syncopal-associated injury; and to administer the vaccine while the patient is lying down if there is a history of syncope or fainting. ADRAC noted the latter recommendation was impractical in school-based settings.

10.2 Vaccine reports

During the period from 24 February to 12 April 2008, 282 reports of vaccine adverse reactions were lodged. This represents about 24% of the reports lodged for the period. A Member noted this was an unusually large number of vaccine reports, most likely due to reports with HPV vaccine which was under intensive, active surveillance.

Copies of all case reports for vaccines received during the period were provided to the Committee.

HPV vaccine reports:

107 of the vaccine reports described reactions to HPV vaccine when given as a single vaccine. The reports were received from NSW (45), QLD (16), SA (12), VIC (11), WA (5), ACT (4), NT (8), TAS (2), or from the sponsor with no State of origin given (4).

Events

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

Vaccine	No. reports
[REDACTED]	[REDACTED]
Human papilloma virus (Gardasil)	107
[REDACTED]	[REDACTED]


Miscarriage

Two reports of miscarriage in females previously vaccinated with HPV vaccine were received (238695 and 237456; see item 11.2.6 of this agenda). In both cases, an association with the vaccine was considered unlikely.

Seizures/convulsions (14 reports)		
Report number	Vaccine/s	Details
238372	Gardasil	22 y.o female experienced a minor fit and loss of consciousness after her first dose. Drowsy for 30 min then recovered.
238405	Gardasil	18 y.o girl fainted, fitted and “eyes rolled back” after vaccination. She recovered within 24 h
238696	Gardasil	15 y.o. girl felt faint, went stiff and had minor fit (for 5-10 sec) soon after first vaccination. Resolved quickly.
239699	Gardasil	23 y.o female felt nauseous, had a minor convulsion, fainted and was dizzy with 2 nd dose of vaccine.
238844	Gardasil	15 year old girl became dizzy within minutes of first vaccination, then she had a seizure, was incontinent of urine; was pale and drowsy on recovery. Has history of fitting/fainting episodes
239274	Gardasil	5 min after vaccination, 12 y.o female felt faint, was pale and nauseous and began to fit. Ambulance officers reported grand mal seizure lasting 40 mins. Not yet recovered at time of reporting.
239309	Gardasil	Report from sponsor of a TV item describing a girl who developed sore arm, chest pain, body tremors and convulsions.
239361	Gardasil	Immediately after second dose, 26 y.o female experienced tonic clonic seizure lasting 10 secs.
239644	Gardasil	18 y.o female showed transient loss of vision, began twitching, lost consciousness for 5 min, and had a tonic seizure after her 2 nd vaccination.
239757	Gardasil	15 y.o girl with history of fitting fainted and fitted (20-30 secs) after vaccination. Reporter suggests it was a vasovagal seizure

Members considered that many of the events coded as ‘seizure’ or ‘convulsion’ in association with HPV vaccine were more correctly described as tonic or clonic movements associated with syncope and it was important to distinguish these from ‘seizure’ or ‘convulsion’ without syncope (see also item 10.3.2, below). Of the events listed in the table, only 238340, 238721, 239107, 239323 and possibly 239309 appeared to be seizure without syncope.

Members note in particular report 239274, which described a 12 year old girl who 5 min after her first doses of hepatitis B and HPV vaccines started to feel faint, was pale and nauseous, and fainted. An ambulance was called and the girl was reported (by ambulance officers) to have had “a grand mal seizure which lasted 40 minutes with tonic/clonic features. Her eyes were seen to be deviating to the right.” The girl continued to experience “short spells of fitting lasting around 4-5 min each time.” Members noted that the patient remained neurologically normal throughout the course of the event and considered the characteristics and time frame of the events were inconsistent with true epileptic-type convulsions. Members agreed with the reporter’s diagnosis of “functional seizures with anxiety” and noted with some concern that the girl had been treated with several barbiturates and benzodiazepines, which was considered excessive.



GBS (0 reports) and other serious reactions in SOC 'nervous system disorder' (11 reports)*		
Report number	Vaccine/s	Details
238381	Gardasil	2 days after vaccination, 16 y.o female developed abdominal pain in lower right. Pain persisted, leg weakness and tingling developed, with back pain. Still has episodes some days worse than others. Also difficulty breathing.
238959	Gardasil	16 y.o female felt tiredness, dizzy and nauseous immediately after vaccination, and 5 min later developed pins and needles in hands. Taken to hospital but recovered later same day.
238962	Human papillomavirus NOS	14 y.o girls felt dizzy and had headache, low BP, fainting, vomiting and malaise after first HPV dose.
238965	Gardasil	19 y.o female had shortness of breath, chest pain and lip tingling after 3 rd HPV dose

239284	Gardasil	1 h after vaccine, 14 y.o girl felt dizzy, sleepy, nauseous, hot and fainted.
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(ie, "A serious adverse drug reaction is any untoward medical occurrence that at any dose results

in: death; is life threatening; requires hospitalisation or prolonged hospitalisation; results in permanent disability”); none of the reactions classified as neurological in association with HPV vaccine (shown above) were considered serious. However, reports 238381 and 239663 were notable.

238851	Gardasil	
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239254	Gardasil, H-B-VAX II	
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Rash, urticaria or pruritus (63 reports)

Note: An onset time of 0 means the reactions occurred on the day of vaccination. NS = not stated.

238285	Gardasil	1
238341	Gardasil	0
238394	Gardasil	11
238420	Gardasil	0
238544	Human Papillomavirus Recombinant Vaccine Quadrivalent	0
238545	Gardasil	0
238566	Gardasil	0
238725	Gardasil	1
238810	Gardasil	0
238812	Gardasil	0
238823	Gardasil	1
238849	Gardasil	1
238995	Gardasil	2
239006	Gardasil	2
239027	Gardasil	4
239031	Gardasil	1
239258	Gardasil	0
239268	Gardasil	2
239275	Gardasil	0
239276	Gardasil	0
239278	Gardasil	0
239282	Gardasil	0
239286	Gardasil	2
239289	Gardasil	0

Rash, urticaria or pruritus (63 reports)

Note: An onset time of 0 means the reactions occurred on the day of vaccination. NS = not stated.

239469	Gardasil	0
239472	Gardasil,	0
239482	Gardasil,	0

239710	Gardasil	0
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10.3.1 Vaginal lesions with HPV vaccine

At the 305th (Dec 07) Meeting, ADRAC reviewed two reports of vaginal lesions in association with HPV vaccine and requested that this ADR be monitored closely. One of the reports discussed at the 305th Meeting (234004) described a 16 year girl who received her 2nd dose of HPV vaccine and developed vaginal swelling and bruising in the evening and, additionally, vaginal blistering the following day. She was also found to have a fever (40°C) in the evening after immunisation. Biopsy of the blister and serology were negative for viruses and the girl was not sexually active.

Follow-up information for this report from a specialist gynaecologist indicated that the girl had been riding an exercise bike in the days preceding vaccination. The specialist considered the lesion to have an inflammatory cause and was not planning further follow-up.

10.3.2 Convulsions with HPV vaccine

In the period covered by this Meeting, HPV vaccine accounted for 10 of the 14 reports of convulsions or seizures (see table above). This brought to 31 (or 3.5% of total reports) the total number of reports of convulsions/seizures with this vaccine (from a total of 891 reports). A case line listing and copies of the originals of the 31 reports of convulsions or seizures in association with HPV vaccine was provided to the Committee.

A Member advised that the majority of the reports described seizures associated with syncope, rather than true seizures associated with neurological disorder. To date, the reports did not suggest a cause for concern and further investigation was not warranted at this stage.

11.2.6 Human papillomavirus vaccine and miscarriage

Report 238695

A 26 year old female who did not know she was pregnant experienced a miscarriage 1.5 months after receiving her first dose of Gardasil. The age of the fetus was not stated.

Report 237456

A female (age not stated) received her second dose of Gardasil at some time in 2007 and experienced a miscarriage in early 2008. No other details were provided.

Both cases above contained insufficient information to allow any assessment of possible causality. It is noted that miscarriage is a relatively common event, occurring in 10-15% of pregnancies. HPV vaccine is 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. ADRAC agreed an association with HPV vaccine was unlikely in cases 238695 and 237456.

