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Minutes of the

Adverse Drug Reactions

Advisory Committee

306th meeting

15 February 2008

[redacted]

8 Summary of reports for review

The line listing of reports lodged in the period covered by this Meeting (16 Nov 07 –04 Jan 08) with proportional reporting ratios was provided. The following associations were highlighted at the Meeting:

Medicine	Adverse reaction	Reports in database (sole suspected)	Comment
[redacted]			
HPV vaccine	Multiple sclerosis relapse	1 (1)	See item 10

[redacted]

10 Vaccines

10.1 Vaccine issues and published articles

10.1.1 HPV vaccine and anaphylaxis – NSW reports

At the previous meeting, the NSW Health Human Papillomavirus (HPV) Vaccination Program Adverse Events Review Panel interim report on cases of anaphylaxis following HPV vaccination in NSW was presented as a late paper. This report was represented for discussion at the current meeting, along with the following overview:

The report reviewed cases of suspected anaphylaxis reported from the NSW schools-based HPV vaccination program. All of these cases have previously been reviewed by ADRAC. Of the ten cases reviewed, the panel concluded there were eight cases of anaphylaxis (2 Brighton level 1, and 6 Brighton level 2). This corresponds to a rate of anaphylaxis of 26.5 per million doses administered (264,650 doses administered; one of the eight anaphylaxis cases was not from the schools-based program). This is considerably higher than previously estimated rates of anaphylaxis in association with Gardasil, which have ranged from 1.8 for Victoria to 11.2 for NSW, with a national rate of 5.1 per million doses administered [data from TGA presentation to NIC meeting, 20 November 2007].

ADRU staff had reviewed the NSW report and raised a number of concerns around the coding of some of the reports. These concerns were discussed out-of-session with the vaccines expert Member of ADRAC and consensus was reached with respect to the reactions that were coded in all of the cases.

ADRAC Members noted there was some discussion between ADRU staff and the ADRAC Member over the definition of 'generalised rash' in relation to case 229316. The Member advised that some definitions consider a rash to be generalised if it appears on two or more sites on the body, but this approach is not adopted universally. ADRAC agreed that the overriding consideration when reviewing reports of allergic reactions is to clearly define at the outset the criteria that will be used and consistently applied to these reports.

10.1.2 Anaphylaxis definitions

The Acting Principal Medical Adviser provided an overview of some of the more commonly used definitions of anaphylaxis and requested the Committee consider the following issues:

There have previously been discussions at ADRAC concerning definitions of anaphylaxis. Some concern has been expressed that some reactions graded as "anaphylaxis" using the Brighton Collaboration definitions would not meet some clinicians' understandings of "anaphylaxis" or "anaphylactic shock".

In Australia, there is a clear impression that HPV vaccine causes a higher rate of presumably immune-based reactions (anaphylaxis, urticaria). In Australia, the TGA and some States have used the Brighton Collaboration criteria for assessing reports of anaphylaxis. Is it possible that the use of these criteria is leading to more ready classification of reactions as anaphylaxis? Also, does use of this definition impact on comparisons with other vaccines?

There are currently at least three sets of definitions of anaphylaxis that might be used in Australia in the context of vaccine monitoring:

1. CIOMS

In 1999, the Council for International Organizations of Medical Sciences (CIOMS) published *"Reporting Adverse Drug Reactions – Definitions of Terms and Criteria for their Use."* Their definitions of anaphylaxis, anaphylactic shock and anaphylactoid reaction as published were the same as included in the published report of their 13th Meeting.

2. Australian Immunisation Handbook

The 8th edition has been in use since 2003. The draft for the 9th edition has been completed and its release is imminent.

3. Brighton Collaboration definitions

See The Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; 25: 5675–5684.

The three definitions are compared in the table below. The comparison highlights that the Brighton Collaboration definition includes a number of clinical manifestations, called "Minor Criteria", which are not included in the CIOMS or Handbook definitions. These particularly have the potential to contribute to reactions meeting the Level 3 of diagnostic certainty.

ADRAC discussion

Issues associated with the apparently greater rate of allergic reactions with HPV vaccine when compared with other vaccines were discussed. Members had previously discussed the difficulties associated with comparing rates of allergic reactions and anaphylaxis with HPV vaccine with rates obtained for other vaccines in Australia and with rates associated with any vaccine in other countries. The current HPV vaccination program was somewhat unique in that it was under intense scrutiny *via* active surveillance programs and specialised Expert Panels. It was also likely that those administering the vaccine were particularly alert to reactions that might be anaphylaxis and were therefore reporting events that might otherwise have not warranted reporting. Despite this, Members considered it was likely that HPV vaccine (Gardasil) was probably more allergenic than many of the other vaccines. The possibility that this was due to the yeast and/or L-histidine components used to manufacture the vaccine was considered but dismissed as being unlikely.

Members considered that the use of the Brighton Classification criteria to assess reports of allergic reactions with HPV vaccine may have resulted in a greater number of reports being classified as 'anaphylaxis' than if another set of criteria had been used. It was also important to note that the assessment of Australian reports of allergic reactions to other vaccines has not been done with reference to the Brighton Collaboration criteria and therefore a comparison of rates of allergic reactions between vaccines is unlikely to be valid. Members agreed it would be an interesting and useful task to re-assess all reports of allergic reactions using the same criteria; but this was beyond the scope of current resources. It was important to also note that other pharmacovigilance organisations around the world almost certainly varied in the criteria they used to classify allergic reactions and therefore any comparison of Australian rates of allergic reactions to HPV vaccine with rates obtained overseas should be done with caution.

The Committee agreed that the use of Brighton Classification criteria to assess rates of anaphylactic reactions to HPV vaccine in Australia may have resulted in greater number of these reports being classified as anaphylaxis than if a different classification system was used. Members considered whether it may be more useful to assess reports of HPV vaccine in terms of 'severe' and 'non-severe' reactions but agreed this would not be a useful or valuable approach.

It was noted that published definitions of anaphylaxis and what is understood by the term anaphylaxis has undergone change over the years. Members agreed that any definition should include a respiratory component and a cardiovascular component but the precise events associated with these systems may be difficult to stipulate.

Despite the difficulties, ADRAC agreed the Brighton Classification criteria remained a useful and workable tool for the assessment of allergic reactions to vaccines and would continue to be utilised by the Committee. However, for reasons mentioned above, a cautious approach would be taken when comparing rates of anaphylaxis that have been determined using these criteria with rates identified using other criteria for anaphylaxis or with rates that have been determined using unidentified criteria.

10.1.3 Items for information

The following papers were noted for information:

[redacted]

[redacted]

- Siegrist C-A *et al*. Human Papilloma virus immunization in adolescent and young adults. A cohort study to illustrate what events might be mistaken for adverse reactions. *Paediatr Infect Dis J* 2007; 26: 979-984.

[redacted]

- Adverse events reported for HPV vaccine. *CMAJ* 2007; 177: 1169-1170

[redacted]

Reports of vaccines other than HPV vaccine

155 of the vaccine reports describe reactions to vaccines other than HPV vaccine given as a single vaccine. 118 of the reports were received from States, Territories or Local Government Councils, 25 were received from health professionals, 5 were from sponsors; 7 were from the Australian Vaccination Network. 117 of the reports related to vaccination of children, 34 related to vaccination of adults, and age was not stated in 4 cases.

There were no deaths reported in association with vaccines. The number of reports received in association with individual vaccines is shown below:

Vaccine	No. reports	Vaccine	No. reports
[redacted]			
		Human papilloma virus (Gardasil)	125

HPV vaccine reports:

125 of the vaccine reports described reactions to HPV vaccine. The reports were received from NSW (27), QLD (26), SA (24), VIC (23), WA (10), ACT (7), NT (2), TAS (1), or from the sponsor with no State of origin given.

All case reports associated with vaccines received during the period covered by this Meeting (16 Nov 2007 to 04 January 2008) were provided to the Committee. Summarised details of particular reactions associated with vaccines are shown in the Tables, below.

Seizures/convulsions (8 reports)		
Report number	**Vaccine/s**	**Details**
[redacted]		
235869	HPV	21 y.o female; no observation by GP, and no treatment required
235992	HPV	27 y.o female also had syncope,
236309	HPV	15 y.o female; 2 weeks after 3rd dose, recovered
[redacted]		
236425	HPV	Age not stated; 2nd dose; also had syncope and disorientation
236427	HPV	Age not stated; reaction onset 1 week after vaccination
236519	HPV	27 y.o female; 2nd dose; has history of seizures

[redacted]

GBS (2 reports) and other serious reactions in SOC 'nervous system disorder' (11reports)*		
Report number	**Vaccine/s**	**Details**
[redacted]		
235453	HPV	16 y.o female, encephalitis, agitation, confusion
235626	HPV	15 y.o female, headache, neck pain, vision blurred
[redacted]		
236434	HPV	24 y.o female; malaise, fatigue, somnolence, feeling abnormal
[redacted]		
236521	HPV	26 y.o female; irritability, myalgia, lethargy, memory impairment, skin exfoliation, disturbance in attention
[redacted]		

Extensive limb swelling (16 reports)		
[redacted]		
236187	Gardasil (Dose 1)	15 y.o female, developed red, bluish-like bruising and swelling from tip of fingers to shoulder
[redacted]		

Rash within 24 h (45 reports) **Note:** 62 reports in this period included 'rash', pruritus' or urticaria' as a reaction term. The 45 reports tabulated are those that indicated or suggested onset time within 24 h.		
Report number	**Vaccine/s**	**Details**
[redacted]		
235393	Gardasil (dose 1 and 2)	Pustular rash day after vaccination
235395	Gardasil	Pruritic rash appeared on thighs, arms, face, back and legs over 4 day period
235397	Gardasil	Erythema multiforme; blotchy red rash about 5 h after vaccine, progressed to welts and blisters on face, limbs and trunk, Also swelling of tongue, hands and feet and mouth ulceration
[redacted]		
235455	Gardasil	Fine raised, red rash over trunk, neck, upper

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		arms, top of legs within 2 hrs of injection.
235507	Gardasil	Urticaria; erythematous dots on both lower legs. Itchy urticarial rash developed on legs the following morning
[redacted]		
235701	Gardasil	Day after vaccination – itch, skin rash, pruritus
[redacted]		
235722	Gardasil	Patient experienced itchy, raised, red rash; also pain in her back, feet and hands, abdominal cramps, shivering, vomiting for 24 hours.
235769	Gardasil (also taking amoxicillin and zolpidem)	Allergic reactions. Patient presented to emergency with rash, felt like her tongue was swollen, swollen hands and feet and itchy throat following 1st dose of Gardasil injection at 1400hrs. Onset of rash at 1900hrs after taking antibiotic (amoxil) and stilnox. Both of which has had before. This was the first dose of this course of amoxyl. Treated with steroid and promethazine
[redacted]		
235848	Gardasil	Generalised, widespread mildly itchy rash. Itchy, red left eye (lateral) within day after vaccination
235858	Gardasil	30 minutes following vaccination began to feel hot with rash appearing on arms and legs.
235861	Gardasil	8-10 hours post vaccination, discrete isolated raised, tender red blotches on both upper arms.
[redacted]		
235864	Gardasil	Rash, oedema of feet and hands. Dark purple rash on legs and arms, resolved 48-72 h.
[redacted]		
235886	Gardasil	Injection site and body rash (after 3rd dose, rash also after 1st and 2nd doses)
[redacted]		

Rash within 24 h (45 reports)

Note: 62 reports in this period included 'rash', pruritus' or urticaria' as a reaction term. The 45 reports tabulated are those that indicated or suggested onset time within 24 h.

[redacted]

235963	Gardasil (also taking venlafaxine and valacilcovir)	Hives 1 h after vaccine

[redacted]

236304	Gardasil	12-24 hours following the 1st dose, fine, pink, erythematous rash ("Morbilliform") on arms, legs, chest, waist. Following 2nd vaccine, swollen itchy hands and feet. No rash on 2nd occasion.

[redacted]

236598	Gardasil	10 min after injection, rash on neck, chest, both arms

[redacted]

236628	Gardasil	Child developed a red, hot, urticarial rash around her neck and small red erythematous rash on trunk approximately 25 minutes after immunisation.
236630	Gardasil	Child developed a rash after her second dose of Gardasil, she had small, very itchy dots on her trunk and back

Rash within 24 h (45 reports) **Note:** 62 reports in this period included 'rash', pruritus' or urticaria' as a reaction term. The 45 reports tabulated are those that indicated or suggested onset time within 24 h.		
[redacted]		
236683	Gardasil	Rash to upper trunk/back and neck - small pink raised spots, itchy.

10.2.1 Allergy reactions and anaphylaxis with HPV vaccine

In recent Meetings, ADRAC has been reviewing in detail all reports involving HPV vaccine that suggest a possible anaphylactic reaction, with a view towards deciding whether the reported reaction is consistent with anaphylaxis using the Brighton Collaboration criteria for assessing degree of certainty. Only one report of this type was identified at the current Meeting, but this case was determined after the Meeting to be identical to a case previously reviewed by the Committee:

Report 236310 (duplicate of reports 232966/232965/232963)

Reports 232966/232965/232963 were discussed previously at the 304th (Nov 07) Meeting. This was a complex case involving three reaction sequences in a 20 year old female. On the same day after administration of Gardasil, the patient experienced 'anaphylactic shock', with symptoms described as 'flushing', 'difficulty breathing', and 'feeling tightness in chest'. The patient also later developed muscle tightness at the injection site and enlarged glands on the side where the vaccine was administered.

At the 304th Meeting, Members discussed *the difficulties in interpreting ambiguous symptoms such as 'flushing' and 'difficulty breathing'; and also commented on the difficulties faced in assessing reports that state a patient experienced 'anaphylaxis' but no associated symptoms are mentioned. The Committee suggested reports of this type should be pursued to determine if more accurate and informative details are available from the reporter.* No further information on this case was contained in the duplicate report considered at the current Meeting and it remained difficult to interpret. **Members again requested that the reporter be contacted and asked to clarify the basis for the diagnosis of 'anaphylactic reaction'.**

In addition, to avoid any confusion in the future, this report will only be referenced by a single ADRAC report number, **232965**.

Allergic reaction with HPV vaccine, zolpidem and amoxicillin

Report 235769

A 21 year old female who received her first dose of Gardasil and also took amoxicillin and zolpidem developed swollen tongue, hands and feet, and itchy throat. The reaction occurred at an unspecified time after she had taken amoxicillin and zolpidem and 5 hours following vaccination.

ADRAC considered an association with HPV vaccine or amoxicillin or both medicines was likely in this case, and an effect of zolpidem could also not be ruled out given the temporal relationship.

10.2.2 Vaginal lesions with HPV vaccine

Report 235391

Two days after her first dose of HPV vaccine (Gardasil), a 17 year old girl (not sexually active) developed "vaginal inflammation that progressed into little cuts and vaginal blistering". The lesions were reported to be very painful and the girl experienced pain on urination but resolved 7 days later.

Report 235631

Twenty-four hours after her first dose of HPV vaccine (Gardasil), a 17 year old girl developed an itchy, fluid-filled blistery rash from her waist to the knees, with severe groin (vaginal) irritation and itch. The rash reportedly started to subside and then flared again.

The Committee had previously commented on a possible early signal for vaginal lesions with HPV vaccine (refer to item 10 of the Minutes of the 305th (Dec 07) Meeting). At that time, it was recommended that ***a review should be undertaken to determine the possibility that there might be an early signal for vulvovaginal lesions with HPV vaccine.*** **Members re-iterated this request and suggested the review should include details of the outcome in each case, and a request for further information from the reporter if warranted and appropriate. Experts in adolescent gynaecological health (such as [redacted] from Victoria) could be approached to provide comment on a possible association and information on the background rate of lesions that have been reported.**

10.2.3 Deep vein thrombosis with HPV vaccine

Report 236307

A 26 year old female who was vaccinated with her second dose of HPV vaccine (Gardasil) and was taking cyproterone acetate/ethynyl oestradiole developed pain on walking and was confirmed to have developed blood clots in her left leg from ankle to groin. Details of the precise interval between vaccination and diagnosis of thrombosis were not provided, but it was most likely to be 1-2 months because the patient's first dose was given about 3-4 month prior to thrombosis being detected. Members considered an association was more likely with the oral contraceptive rather than the vaccine.

ADRAC agreed it was unlikely this case involved HPV vaccine.

Report 236663

A 21 year old female who was vaccinated with her second dose of HPV vaccine (Gardasil) and was taking oral contraceptives (not specified) was found to have deep vein thrombosis (and anti-phospholipid syndrome and juvenile arthritis). The diagnosis was made 1 month after vaccination, but as with the previous case, Members considered an association was more likely with the hormone contraceptive than with the vaccine.

ADRAC agreed it was unlikely this case involved HPV vaccine.

10.2.4 Pancytopenia with HPV vaccine

Report 236414

Three weeks following a third vaccination with HPV vaccine (Gardasil), a 17 year old female developed pancytopenia with fever, splenomegaly, myalgia and retroperitoneal lymphadenopathy. ADRAC was not convinced of an association in this case. It was notable that the reporter in this case was a respiratory specialist; and that microbial infections including measles are also associated with pancytopenia.

10.2.5 Acute disseminated encephalomyelitis with HPV vaccine

Report 235453

Three months after vaccination with a second dose of HPV vaccine (Gardasil), a 17 year old female presented with agitation, confusion and ataxia and her MRI scan was consistent with acute disseminated encephalomyelitis. Members noted this report with interest, but it was unclear whether there was an association with the vaccine.

[redacted]

14 Australian media

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

[redacted]

- HPV vaccine – panic over extent of ADRs and pain; more information call

[redacted]