Adverse Drug Reactions Advisory Committee

Out-of-Session Teleconference Meeting on Human Papilloma Virus Vaccine

3.30-5.00 pm, Wednesday 4th July 2007

Ratified at the 302nd ADRAC Meeting (August 2007)

Those present were:

[redacted]	Chairman
[redacted]	Member
[redacted]	Member
[redacted]	Member
[redacted]	Member
[redacted]	[redacted] ADRU. Secretary, ADRAC
[redacted]	[redacted] ADRU
[redacted] s22	[redacted] DSEB
	s22 [redacted] TGA
[redacted]	[redacted] ADRAC
[redacted]	ADRU

Background

An out-of-session Meeting of the ADRAC was convened at short notice to discuss concerns from the NSW Health Department regarding the safety of the human papilloma virus (HPV) vaccine, Gardasil.

Gardasil was registered in June 2006 for the following indication: *"Gardasil is indicated in females aged 9 to 26 years* for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by Human Papillomavirus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine). GARDASIL is indicated in males aged 9 to 15 years for the prevention of infection caused by Human Papillomavirus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine). *Immunogenicity studies have been conducted to link efficacy in females aged 16 to 26 years to the younger populations."*

Three separate doses are required, with the second and third doses given 2 and 6 months, respectively, after the first dose.

From 1 April 2007, HPV vaccine has been provided at no cost to girls aged 12-18 years through a school-based, government-funded program. A broader, community-based program for females aged up to 26 years old has commenced more recently. To date, Gardasil is the only government-subsidised HPV vaccine available in Australia.

The NSW Chief Medical Officer recently alerted the Department of Health and Ageing to 47 reports of adverse reactions to Gardasil, experienced by school girls taking part in the HPV immunisation program. These reports were received from various health professionals around NSW and were reviewed by a NSW Government Expert Panel comprising of academic immunologists. The Panel was particularly concerned about 7 reports judged to be anaphylaxis.

The NSW Health Department subsequently sought advice from the Department of Health and Ageing regarding any requirements for action or review. TGA input was sought as part of the Federal Government's action on this matter.

167,000 doses of Gardasil have been administered to girls in NSW since the school-based program commenced. These were first or second doses, with no third doses yet administered. Vaccine used in NSW was derived from 4 batches of 2 bulk vaccine lots (with 3 of the batches derived from 1 bulk lot). TGA is currently testing batch samples to determine if there are issues relating to quality, such as the presence of contaminants that might be expected to cause adverse reactions. TGA also requested the NSW Government provide samples of vaccine specifically associated with reported adverse reactions, and these will also be tested for quality.

ADRAC noted that 50% of the same vaccine bulk lots used in NSW had been distributed to the remaining Australian States and Territories. Presumably, the number of vaccine doses administered through school-based programs outside NSW was at least as high (and probably greater) as the number administered in NSW. According to the NSW Health Department, only 3 cases of anaphylaxis have been reported in States and Territories outside NSW, suggesting issues relating to possible vaccine-associated anaphylaxis may be confined to NSW. In this context, it was noted that issues of anaphylaxis with Gardasil had not emerged in any other country, including the USA.

ADRAC agreed it was essential the TGA, in association with other Government agencies and the sponsor, conduct intensive investigations to firstly determine if there is a safety issue regarding Gardasil in NSW; and, if problems are confirmed, to take immediate action to manage these problems. As part of the investigations, ADRAC had been requested to independently review the 47 reports of adverse reactions to Gardasil from NSW and advise if there are important safety signals that require immediate attention. The Committee noted that the ADRU had also reviewed the NSW reports, independently of the NSW Expert Panel review.

Review of NSW reports on Gardasil

ADRAC referred to a tabulated summary of the 47 cases reported in NSW, provided by the NSW Health Department. Original reports describing these reactions had not been supplied, but it was noted that TGA had requested the NSW Government obtain these as part of the investigations.

Prior to assessing the reports, ADRAC sought and received confirmation that all cases involved administration of the Gardasil brand of HPV vaccine and that no other vaccines had been administered concomitantly. ADRAC noted that vaccine injections had been given mainly by clinical nurses, presumably according to a standard protocol. There was no information available on the circumstances or situations (including venues) in which vaccine administration had taken place.

Anaphylaxis – definition and degree of certainty

In reviewing the 47 reports, ADRAC applied the Brighton Collaboration case definition of anaphylaxis (see Attachment 1). This system allows a decision to be made on the level of certainty that a specific event is in fact anaphylaxis, based on the presence of various clinical signs and symptoms. The case definition is, as far as is possible, based on objective, measurable, physiological signs encompassing 3 organ systems (respiratory, cardiovascular and gastrointestinal) and taking into account the severity of particular clinical signs and symptoms. The validity of conclusions regarding certainty that an event is true anaphylaxis is highly dependent on the diagnostic accuracy of the clinical signs and symptoms. Therefore, this system is not necessarily wholly objective or accurate, particularly when used to define events on the basis of third party

reports. Members noted the Brighton Collaboration case definition is not intended to provide information on causality or severity of event.

Members were concerned that the quality and extent of the data available on the NSW cases would limit the accuracy of the diagnostic classification of anaphylaxis events. This consideration was important as Members reviewed the reports, but it was agreed that the descriptions of events would be regarded as accurate unless there was information to clearly indicate otherwise.

Based on the Brighton Collaboration case definition, anaphylaxis can be diagnosed according to 3 levels of certainty, with Level 1 having the highest degree of certainty and Level 3 having the least. ADRAC noted that the Brighton attribution system differed somewhat from the attribution system used usually by ADRAC. However, Members agreed that Level 1 could be considered analogous to 'certain', Level 2 was analogous to 'possible' and Level 3 was analogous to 'unlikely' in terms of defining whether or not an event had occurred.

Of the 47 cases, ADRAC considered there were 8 that should be assessed further to decide on a level of certainty that they were in fact anaphylaxis:

Reports of possible anaphylaxis

Case 2, s22 ***16 May 08, reaction onset 10 min:*** *"16 year old girl who experienced severe vomiting within 10 min of injection. She vomited mucous and blood. She stated feelings of impending doom and difficulty breathing. Respiratory stridor, pulse 68, colour good, IMI adrenaline given. Hospitalised, discharged pm at patient's request."*

With the exception of respiratory stridor, the reported respiratory, cardiovascular and gastrointestinal signs reported were all minor criteria according to the Brighton Collaboration case definition and this case would not fit the description of anaphylaxis. **However, the presence of stridor, a major criterion according to the Brighton classification system, suggests there is a Level 2 degree of certainty that this was a case of anaphylaxis.**

Members commented on the difficulty of interpreting descriptions such as 'difficulty breathing', as this was a subjective rather than an objective phrase. Members also expressed some doubt as to whether respiratory stridor had in fact developed. It was noted that the girl was hospitalised, treated with adrenaline and recovered.

Event 7, s22 ***11 May 07: Onset 60 mins:*** *"1 hour post vaccination developed shortness of breath, felt weak, stomach ache, back ache, itchy eyes, blurred vision, pulse 100/min. Transferred to hospital. No treatment. Discharged."*

ADRAC noted the presence of several minor signs (shortness of breath, itchy eyes, abdominal pain) which may be consistent with anaphylaxis, but there was no major symptom associated usually with disorder. ADRAC noted that all of the minor symptoms were non-specific and non-measurable. This case would ideally be one to follow-up in a clinic by diagnosticians who could perform appropriate tests to determine the exact nature and aetiology of the symptoms. The absence of confirmatory testing contributed to ADRAC's view that this case was equivocal. **ADRAC agreed there was a Level 3 degree of certainty that this was a case of anaphylaxis.**

Case 12, s22 ***2 May 07, onset immediate:*** *"Immediately post vaccination nauseous, blotchy itchy rash on face, laboured breathing. History of adrenaline following tetanus vaccine. Adrenaline given. Improved. Transferred to hospital. 1 day post vaccination itchy all over body and pins and needles to hands."*

The description of *'blotchy itchy rash on face'* did not entirely fit within with the criteria for a major or a minor dermatological reaction according to the Brighton Collaboration criteria. Further, the development of an all-over body itch 1 day post-vaccination was not consistent with the dermatological reaction expected if this was an anaphylactic reaction. Members suggested the phrase 'laboured breathing' was not consistent with an anaphylactic response, which would more typically involve wheezing and/or stridor.

ADRAC considered there was considerable doubt that this was a case of anaphylaxis. Based on the presence of a possible, minor skin, respiratory and gastrointestinal manifestations, **the Committee agreed there was a Level 3 degree of certainty that this was a case of anaphylaxis.**

Case 15, s22 ***24-May-07, onset 10 min:*** *"red mottled face to waist. Nauseated, cyanosed, difficulty breathing. Throat and tongue restricted. No stridor cough developing. Adrenaline 0.5 mL given with no improvement. Further 0.5 mL given 5 min later. Improved. Transferred to hospital."*

Members suggested the description of the skin manifestation (mottled face to waist) would be consistent with generalised erythema. ADRAC noted the term 'cyanosed' was mentioned in the report, although the absence of stridor was specifically recorded. Nevertheless, it was considered likely that a major respiratory symptom had developed. In view of the major respiratory manifestation and minor gastrointestinal and skin manifestations, **the Committee agreed there was a Level 2 degree of certainty that this was a case of anaphylaxis.**

Case 32, s22 ***7 Jun 07, onset 5 min:*** *"5 Min post vaccine collapsed. Face flushed spreading to hairline. Tachycardic, not responding. Became agitated, nauseated. Mild shortness of breath. 0.5 mL adrenaline given with little effect. Dose repeated. Transferred to hospital. Discharged pm post EEG."*

With the exception of 'collapse', all reported symptoms were minor and none was clearly consistent with a hypersensitivity response. The circumstances and underlying cause of the collapse were unclear, but they were unlikely to have involved the immune system. The symptoms were more consistent with a vaso-vagal stress response. **ADRAC considered this was not a case of anaphylaxis.**

Case 33, s22 ***7-Jun-07, onset 'within mins':*** *"no immediate reaction. Within mins post vaccine (dose 2) felt funny, nauseated, blotches noted on neck. Urticarial rash developed. Tightness in throat. Colour poor. 0.5 mL adrenaline give. Transferred to hospital. No further treatment. Discharged."*

This report document a minor dermatological response (localised urticaria), a minor respiratory component (tightness in the throat) and a minor gastrointestinal component (nauseated). On this basis, **the Committee agreed there was a low (Level 3) degree of certainty that this was a case of anaphylaxis.**

Case 37, s22 ***19-Jun-07, onset 5 mins:*** *"5 mins post vaccine (dose 2) felt faint and dizzy, coherent and talking. Commenced to grab her neck and gasping, distressed, nauseous. Symptoms settled momentarily. Difficulty with breathing returned. Adrenaline 0.5 mL given. Transferred to hospital"*

The symptoms reported in this case were more consistent with a vaso-vagal reaction rather than with anaphylaxis. There were no signs that could be attributed to a hypersensitivity reaction. **ADRAC considered this was not a case of anaphylaxis.**

Case 46, s22 ***21-Jun-07, onset 10 mins:*** *"returned to clinic 10 mins post vaccine (dose 2) with throat tightness and slight dizziness. Urticarial blotchy rash across face and upper chest noted. Anxiety noted. 0.5 mL adrenaline given. Transferred to hospital."*

Members debated whether *urticarial blotchy rash across face and upper chest* was intended to convey generalised or localised rash. Assuming the rash was generalised, this presented a major criteria for defining anaphylaxis. However the respiratory component was minor (throat tightness) and no gastrointestinal component was mentioned. **On this basis, ADRAC considered there was a Level 2 degree of certainty that this was a case of anaphylaxis.**

Discussion

Overall, ADRAC considered there were 6 cases of possible anaphylaxis – 3 with Level 2 degree of certainty and 3 with Level 3 degree of certainty. Of the reports considered, none was considered a Brighton Level 1 (ie, certain) case of anaphylaxis.

Members were mindful that uncertainties about the accuracy of the reported symptoms prevented a definitive conclusion to be made for this review. However, the Committee was confident that the information provided was of sufficient quality to allow the detection of true cases of anaphylaxis. The fact that no Brighton Level 1 cases were identified was reassuring. Members also noted that all suspected cases of anaphylaxis had been treated appropriately and recovered fully.

ADRAC noted that anaphylaxis is a rare event associated with most vaccines, with an incidence ranging from 1 in 100,000 to 1 in 1,000,000 doses depending on the vaccine (eg, see Bohkle *et al., Pediatrics*, 2003; 112: 815-820). Assuming all 6 cases reported to NSW were in fact anaphylaxis, this would suggest a maximum reported rate of 3.6×10^{-5} or about 1 in 27,833 Gardasil doses. The sponsor had reported an anaphylaxis rate with Gardasil of 10 in 10.5 million doses, based on world-wide data. Therefore, if it was verified, the incidence in NSW would be over 10 fold greater than the world-wide incidence. On the other hand, the true rate could be much lower because none of the NSW cases of anaphylaxis are certain. To put the data into better context, ADRAC suggested information should be obtained on the rates of vaccine-associated anaphylaxis events from large, properly conducted, controlled clinical trials of vaccines with established safety profiles.

Overall, ADRAC agreed that the signal for anaphylaxis emerging from NSW did not warrant immediate action to alert the public. However, it was necessary to conduct further investigations into the safety of Gardasil in NSW to ensure that all safety measures were in place and operating effectively.

It was important that the vaccine was being administered in strict accordance to appropriate protocols, and that appropriate monitoring was being undertaken by suitably experienced health professionals. **ADRAC considered it was possible that factors associated with the reporters may have had a substantial impact on the nature of reports from NSW, but this was yet to be investigated.**

In view of the importance of ensuring accurate data are obtained on events in association with HPV vaccine, **ADRAC recommended that patients with suspected allergic reactions should be followed up in specialised allergy or immunisation clinics established to provide a clinical assessment of reactions to HPV vaccine.** It was anticipated that these clinics would have a role in

following-up and verifying cases of suspected serious reactions, including anaphylaxis. As a result, these clinics would be well-placed to collect post-market information on the safety of HPV vaccine and thereby provide a service of benefit to the public as well as to individuals.

It was also possible that the vaccine was being administered in communal venues (such as school halls) that fostered an atmosphere leading to an increased incidence of vaso-vagal and hysterical conversion reactions. This situation had been reported with the Gardasil school-based vaccination program in Victoria, but it was unclear if similar events had occurred in NSW. A Member advised that studies had been conducted in Australia to determine the rate of reactions in the context of mass, school-based vaccination programs. **ADRAC suggested the NSW reports may need to be reviewed against a background of reaction rates found for vaccines in other school-based vaccination programs.**

It was noted that the Gardasil PI included information on the potential for anaphylaxis. Members suggested this document and other literature on Gardasil should be reviewed to determine it contained adequate information on the risks associated with the vaccine, and appropriate advice regarding monitoring those who have been vaccinated. The sponsor of Gardasil could also be requested to issue general information on safe vaccine practice, to remind practitioners about the importance of adhering to standard vaccine protocols.

ADRAC suggested the product literature, including the PI, CMI and patient/parent consent information should be reviewed to ensure it drew adequate attention to the risks of anaphylaxis and provided sufficient information on post-vaccination monitoring and on the management of symptoms if they occurred.

Neurological and other reactions

ADRAC noted that neurological reactions have previously been a concern with some vaccines and this issue is of particular concern to the public. Two of the 47 NSW reports described in the summary of cases were listed as suspected cases of Bell's palsy:

Case 10 s22 [redacted] reaction onset 40 hours after vaccination) *"swollen glands on opposite side of vaccination site. Right eye red and itchy. [5 days after vaccination], the eye swollen and closed, right side of face has dropped. Dr diagnosed ?Bell's palsy. Left eye now swelling. Child generally unwell."* The patient recovered.

Case 26 s22 [redacted] onset immediate) *"On presentation for dose 2, child reported left sided facial numbness and slight drooping of lips when smiling. Symptoms began immediately after vaccination, Resolved in 5 days with no treatment. Dose 2 not given."*

ADRAC was not convinced that either case was in fact Bell's palsy. In the absence of other signs suggesting neurological involvement, symptoms of 'drooping' or 'dropped' face were likely to be associated with angioedema rather palsy. The reaction onset and resolution times for case 26 were inconsistent with Bell's palsy, while a more likely cause of the symptoms and signs described in case 10 was an allergic reaction with associated oedema. Overall, there was no evidence based on the 47 reports to NSW for a neurological signal with Gardasil.

Other reactions reported in association with Gardasil were consistent with those expected in the target population and/or with vaccines. In particular, a relatively high incidence of vaso-vagal and conversion reactions would be expected given the context of the current immunisation program. However, to determine whether or not the rate of particular reactions is unusual, **ADRAC**

suggested the NSW reports should be reviewed in the context of large, controlled studies of vaccines with well-established safety profiles.

Conclusion

On the basis of reports reviewed at this Meeting, ADRAC agreed there is no immediate requirement to alert the public to safety issues with Gardasil vaccine. Investigations should continue to determine if there is a NSW-specific safety issue related to Gardasil. Product literature intended for Gardasil prescribers and consumers should be reviewed to ensure it adequately describes the risks and requirements for monitoring and management of symptoms. The sponsor should write to GPs advising of changes to the PI, and reminding them to maintain vigilance and monitor patients after vaccination. Information on safe immunisation practices should be included with this correspondence. The Government should ensure that adequate post-market programs are in place to monitor the safety of HPV vaccine.

ADRAC requested this issue be kept on the agenda as a standing item until further notice.

Attachment 1:

Extracts from: ***The Brighton Collaboration Allergic Reaction Working Group: Anaphylaxis as an Adverse Event Following Immunization Case Definition & Guidelines for Data Collection, Analysis, and Presentation. (manuscript for publication)***

Case Definition of Anaphylaxis

Anaphylaxis is a clinical syndrome characterised by
• sudden onset AND
• rapid progression of signs and symptoms AND
• involving multiple (=2) organ systems, as follows:

Level 1 of diagnostic certainty • ≥ 1 major dermatological AND • ≥ 1 major cardiovascular AND/OR = 1 major respiratory criterion
Level 2 of diagnostic certainty • ≥ 1 major cardiovascular AND =1 major respiratory criterion OR • ≥ 1 major cardiovascular OR respiratory criterion AND • ≥ 1 minor criterion involving = 1 different system (other than cardiovascular or respiratory systems) OR • ≥ 1 major dermatologic AND = 1 minor cardiovascular AND/OR minor respiratory criterion
Level 3 of diagnostic certainty • ≥ 1 minor cardiovascular OR respiratory criterion AND • ≥ 1 minor criterion from each of = 2 different systems/categories

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

Major and Minor Criteria used in the Case Definition for the Diagnosis of Anaphylaxis.

MAJOR CRITERIA

dermatologic or mucosal	• generalised urticaria (hives) or Generalised erythema • angioedema*, localised or generalised • generalised pruritus with skin rash
cardiovascular	• hypotension, based on a measurement • clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: o tachycardia o capillary refill time > 3 sec o reduced central pulse volume o decreased level of consciousness or loss of consciousness
respiratory	• bilateral wheeze (bronchospasm) • stridor • obvious upper airway swelling (tongue, throat, uvula or larynx) • respiratory distress – 2 or more of the following: o tachypnoea o increased use of accessory respiratory muscles (sternocleidomastoid, intercostal etc) o recession o cyanosis o grunting

* not hereditary angioedema

MINOR CRITERIA

dermatologic or mucosal	• generalised pruritus without skin rash • generalised prickle sensation • localised injection site urticaria • red and itchy eyes
cardiovascular	• reduced peripheral circulation as indicated by the combination of at least 2 of: - tachycardia and - a capillary refill time of >3 seconds without hypotension - a decreased level of consciousness
respiratory	• persistent dry cough • hoarse voice • difficulty breathing without wheeze or stridor • sensation of throat closure • sneezing, rhinorrhea
gastrointestinal	• diarrhoea • abdominal pain • nausea • vomiting
laboratory	• Mast Cell Tryptase elevation > upper normal limit