Minutes of the

Adverse Drug Reactions

Advisory Committee

305th meeting

14 December 2007

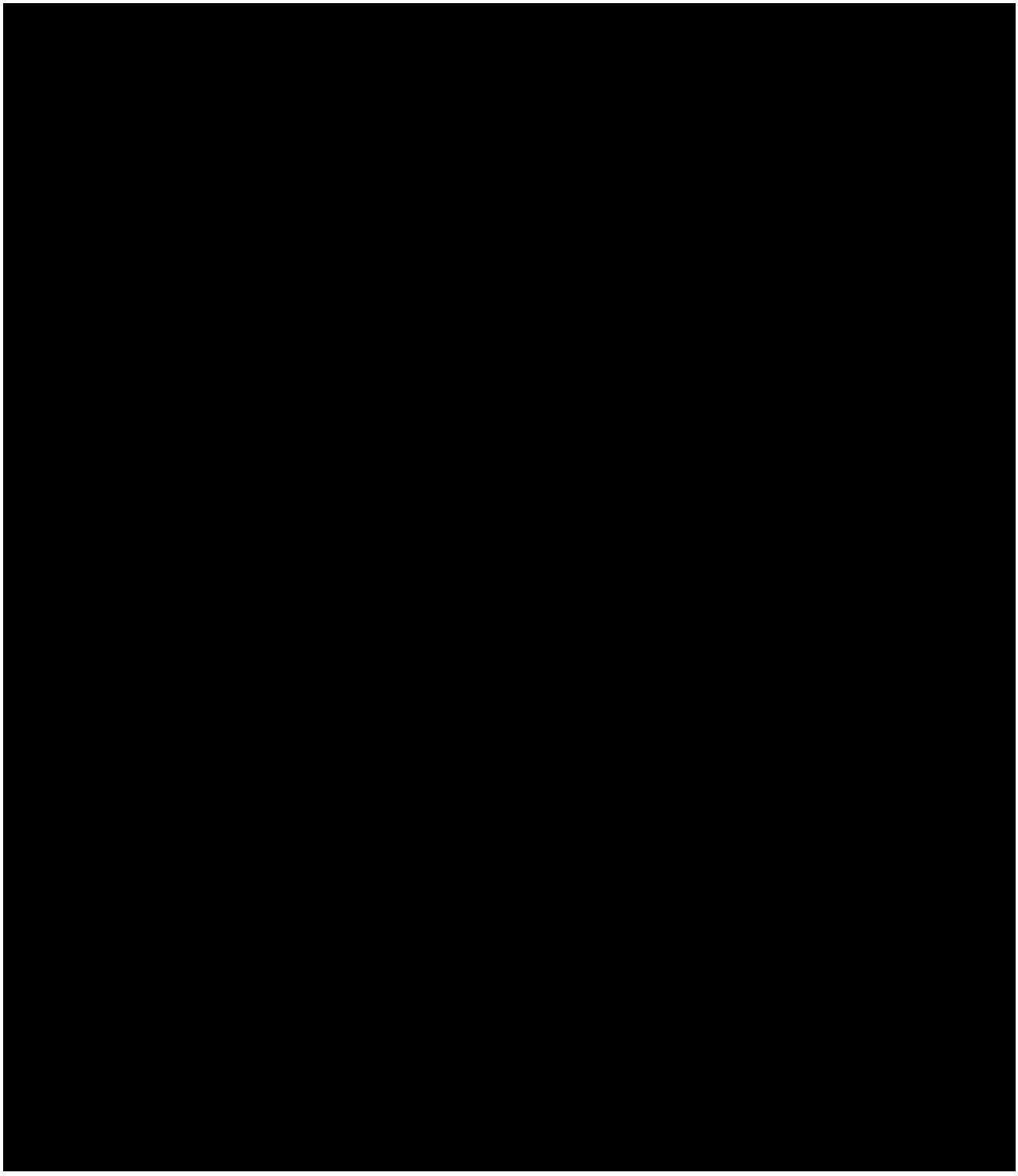
[redacted]

8 Summary of reports for review

The line listing of reports lodged in the period covered by this Meeting (1 October – 15 November 2007) with proportional reporting ratios was provided. The following associations were highlighted at the Meeting:

Medicine	Adverse reaction	Reports in database (sole suspected)	Comment
[redacted]			

Medicine	Adverse reaction	Reports in database (sole suspected)	Comment
[redacted]			
HPV vaccine	Guillain-Barre syndrome Haemolytic anaemia Neuropathy peripheral Optic neuritis Pancreatitis	2 (2) 103 (92) 83 (76) 1 (1) 2 (2)	See item 10.
[redacted]			



10.2 Vaccine reports

At this Meeting (covering the 6-week period from 1 October to 15 November), ADRAC received 254 reports of vaccine adverse reactions. This represents 20% of total reports lodged for the period. Case reports of all vaccines submitted in the period covered by this Meeting were provided to ADRAC. Summarised details of reactions associated with individual vaccines are shown in the Table, below.

Reports of vaccines other than HPV vaccine

129 of the vaccine reports describe reactions to vaccines other than HPV vaccine given as a single vaccine. About 67% of the reports were received from States, Territories or Local

Government Councils, 21% were received from health professionals, 11% were from sponsors; 3 were from the AME line and 1 was from received directly a consumer. 82% of the reports related to vaccination of children; 18% related to vaccination of adults.

HPV vaccine reports:

125 of the vaccine reports described reactions to HPV vaccine. The reports were received from SA (27), NSW (27), VIC (19), QLD (32), ACT (6), WA (10), TAS (2), or from the sponsor with no State of origin given (2).

Members noted that an on-going review of all reports to HPV vaccine was being undertaken by ADRU staff in association with an ADRAC Member, and that information on the post-market safety of HPV vaccine had been provided recently by the TGA to Australian State and Territory Departments. Members also noted a letter from the A/g Principal Medical Adviser to the Australian Technical Advisory Group on Immunisation (ATAGI) and to Australian jurisdictions, providing details of the national reporting of suspected adverse events following immunisation with 4- valent HPV vaccine. A response to this letter had been received from ATAGI was noted for information.

Members also noted the following late paper: an *Interim report of the NSW Health Human Papillomavirus (HPV) Vaccination Program Adverse Event Review Panel* on *Cases of anaphylaxis following HPV vaccination*. This report had been received only recently by the ADRU and had not yet been considered by the Unit. It was anticipated this report would be re-presented at the next ADRAC Meeting when Members would have more time to review it.

Vaccine	*No. reports	Inject. site reaction	Rash/ Pruritus/ urticaria	Convuls-ion /seizure	Fever/ pyrexia	Dyspnoea / apnoea	HHE	Other notable reports/important reactions / comments
[redacted]								
Human papilloma virus (Gardasil)	130: cases	30	36 cases.	s22 ?	15 cases	s22		Guillain-Barre Syndrome: s22 , polyarthritis, ANA +ve: s22 pancreatitis: s22 rheumatoid/ polyarthritis: s22 guttate psoriasis: s22 57 reports describing a term under the SOC 'nervous systems disorder' - see Paper LP10.4
[redacted]								

*Note: The database report used to compile this table counts sequences (ie, unique report numbers given to 2 or more events in one individual patient) as separate reports. Therefore, the number of reports shown here may not precisely reflect the number of reports describing individual patients.

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 as defined by the Brighton Collaboration. Only one report of this type was identified at the current Meeting:

Report s22 [redacted]

This described a 15 year old girl who was given HPV vaccine (right arm; 3rd dose) and DTPa vaccine (left arm) sequentially during the same visit to a school-based immunisation clinic. After an unremarkable observation time of 30 min she was sent back to class.

About 90 min after immunisation, the girl presented to the clinic nurse with a rash on the HPV vaccine-injected arm, localised rash on the back of her knee, and (reported later) tightness in her throat. The rash on her arm was described variously in the report as 'a large hive-like itchy spot' and as 'a large bright red, well defined rash on the top section of right arm extending from shoulder to elbow but not involving the circumference of the limb, red area was itchy and hot to touch'. An itchy rash was reportedly also present on the 'upper chest below her throat' but this was not described in detail. Respiratory symptoms were described in the report as 'tightness in her throat', 'throat felling funny' and 'having trouble swallowing'.

The girl was taken to a GP who measured her blood pressure and temperature (details not provided) and administered adrenaline, cortisone and promethazine. The girl developed a headache later that night and the rash was still present on her arm the following morning. She reportedly felt unwell (headache, lethargy) for 1 week after immunisation and had an injection site lesion (hard red lump the size of a 20 cent piece) for 2 weeks before recovering fully. A history of allergic reactions to vaccines and a recently identified allergy to bee stings were noted in the report.

ADRAC noted that the girl had been given DTPa vaccine at the same time as the HPV vaccine, therefore it was not possible to determine which vaccine/s had caused the reactions other than those directly at the specific site of injection.

The report provided various descriptions of the extent of the rash, but in the absence of a definitive description, Members agreed the rash could be consistent with 'generalised pruritus with skin rash', which is a major dermatological characteristic according to Brighton Collaboration criteria. The respiratory symptoms were also ill-defined but there was no indication for development of major symptoms such as stridor, wheeze or shortness of breath. At most, the respiratory symptoms were consistent with a minor characteristic, such as 'sensation of throat closure'. On this basis, there was a Level 2 degree of certainty that the reaction was anaphylaxis, as defined by the Brighton Collaboration.

Members noted the report contained no details of the GP's assessment of this case (including no details of BP and temperature monitoring), but it was also noted that the treatment given by the GP was consistent with standard treatment of anaphylaxis. Members agreed this was probably a conservative, precautionary approach on the part of the GP and no assumptions about the nature of the reaction could be made on the basis of the treatment in this case.

Members suggested a more conclusive assessment of this case could be made if more definitive information about the symptoms was available. In particular, it would have been of value to have information from the GP. In the absence of this and based solely on the description of a (possibly) major dermatological and a minor respiratory component, ADRAC agreed this case was, at most,

consistent with a Level 2 degree of certainty that the reaction was anaphylaxis, as defined by the Brighton Collaboration. However, the systemic components of the reaction could have been associated with either or both HPV and DTPa vaccines, and the symptoms could equally be defined as an acute allergic reaction to either or both these vaccines.

Report s22 [redacted]

This report described 'acute generalised rash', 'sweats/dizziness' and facial swelling' 1 h after the 2nd dose of HPV vaccine in an 18 year old female with a history of mild asthma. She recovered after treatment with promethazine and cyproheptadine.

The reporter had suggested this was a case of 'mild anaphylaxis'. However, given the absence of respiratory or cardiovascular symptoms, Members suggested this (report [redacted]) did not describe anaphylaxis but was most likely a case of generalised allergic reaction with urticaria and angioedema. It was noted that treatment with adrenalin was not required in this case.

10.2.2 Vaginal lesions with HPV vaccine

Report s22 [redacted]

A 16 year girl who received her 2nd dose of HPV vaccine 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.

Report s22 [redacted]

A 17 year old female who received HPV vaccine 2 weeks previously developed severe, deep genital ulcers on her labia and perineum. Serology was negative for viruses and she had one sexual partner, who was also negative for herpes simplex virus.

Members noted that ADRAC had received several additional reports describing vulvovaginal lesions in females given HPV vaccine. At this stage, it was not clear if there was an association with the vaccine or if the incidence of these lesions was consistent with background rate. Members commented on the possibility that vaginal blistering with HPV vaccine were similar to a fixed drug reaction; previous exposure to the vaccine was reported in case s22 [redacted] but it was not clear if there was blistering or previous exposure in case s22 [redacted]

Members suggested a review should be undertaken to determine the possibility that there might be an early signal for vulvovaginal lesions with HPV vaccine.

10.2.3 Pancreatitis with HPV vaccine

Report s22 [redacted]

A 26 year old female who received HPV vaccine developed generalised rash and was treated with promethazine and doxycycline 2 days later. On day 3 after vaccination, she developed epigastric pain and fever and was found to have increased amylase and lipase levels. Pancreatitis was confirmed by CT scan and she remained hospitalised at the time of reporting (about 2 weeks after vaccination).

Members noted there was no obvious biologically plausible mechanism by which HPV vaccine could be expected to case pancreatitis, although an auto-immune mechanism may be possible. It was noted that the patient in this case had also received doxycycline which may have played a role in this case, although an association between doxycycline and pancreatitis is not recognised (according to the PI). The patient was also taking ranitidine, but this was not a suspected drug.

At this stage, it was not clear if there was a plausible association between the medicine/s and pancreatitis in this case. However, given that similar events had been reported or alluded to in others given HPV vaccine (see below), **ADRAC suggested a watching brief should be maintained for pancreatitis and related reactions with HPV vaccine.**

Report s22

A 24 year old female who received her first dose of HPV vaccine 6 weeks previously developed pancreatitis and was recovering in hospital. The reporter noted an awareness of several other cases of pancreatitis in females given HPV vaccine, including another case admitted to the same hospital as case s22 With the exception of the 2 reports reviewed at the current Meeting (involving patients from different States), ADRAC had not received other reports describing pancreatitis with HPV vaccine.

Given the long interval between vaccination and development of the disorder and the lack of reported details about events (such as alcohol and other medicine use) in the intervening time, Members were not convinced there was an association between HPV vaccine and the development of pancreatitis in this specific case. On the other hand, if an auto-immune mechanism was operating, a delayed reaction would not be unexpected.

Members agreed it was too early to conclude whether or not there is an association between HPV vaccine and pancreatitis and re-confirmed the suggestion that this should be included on the list of watching briefs.

10.2.4 Isolated reactions of interest with HPV vaccine

A Member drew attention to the following reports of interesting reactions to HPV vaccine:

- Report s22 Severe idiopathic thrombocytopenic purpura in a 16 year old girl (although according to dates in the report, the disorder was identified about 4 months after the first dose and 2 weeks before the 2nd and 3rd doses of the vaccine);
- s22 haemolytic anaemia requiring transfusion in an 18 year old female who had been vaccinated with HPV vaccine 2 weeks previously;
- s22 Guillain Barre Syndrome in a 17 year old female who received her 2nd dose of HPV vaccine 1 month previously (the girl had given her first ever blood donation the day prior to GBS developing);
- s22 peripheral neuropathy (bilateral ascending sensory loss in lower limbs. Decrease in sensation to all modalities, lower legs to knees. She had normal knee, ankle and plantar reflexes) in a 16 year old female 4 weeks after receiving her 2nd dose of HPV vaccine;
- s22 Acute macular neuroretinopathy (blurred vision, left greater than right, associated with scotomata) in a 24 year old female who had been given her first dose of HPV vaccine. The reporter did not provide details of the time between drug administration and reaction onset, but it was noted that the patient was just recovering from a viral infection.

ADRAC agreed the reports above were of interest and of some concern. However, at this stage, it was not clear if there was or was not a casual relationship with HPV vaccine in any of the cases. The Committee would continue its close scrutiny of reports with this vaccine.

10.2.5 Overview of ADRAC reports with HPV vaccine

The acting Principal Medical Adviser provided to the Committee an overview of the reports of ADRs to HPV vaccine received to date by the TGA. The same information had been conveyed to relevant Health Authorities in Australian States and Territories and presented at a recent meeting of the National Immunisation Centre. Members were also advised that information on the Australian experience with HPV vaccine had recently been posted on the TGA website.

ADRAC noted that the reported rates of anaphylactic reactions to HPV vaccines appeared to be in the order of 10-20 times greater with HPV vaccine than the rates reported usually for vaccines, and they were disproportionately greater in NSW than in other areas. Reports of other allergic reactions such as rash also appeared to be greater with HPV vaccine but the distribution of these appeared to be similar amongst all Australian regions. In other respects, the ADR profile of HPV vaccine was similar to that observed with other vaccines.

An overall high reporting rate for HPV vaccine was not unexpected given the associated intensive and thorough surveillance monitoring programs established specifically for this purpose. However, the HPV vaccine (Gardasil) did appear to be more allergenic than other vaccines.

Members discussed possible factors that may contribute to the apparent differences in reported rates of anaphylaxis with HPV vaccine than with other vaccines. It was important to note that there was not a uniformly applied case definition for 'anaphylaxis' and that many of these reactions reported with HPV vaccine were not in fact the acute, life-threatening, multi-organ, anaphylactic shock-type reaction that is most often and traditionally associated with the term anaphylaxis. In an attempt to provide a consistent and standard approach to identifying reports of anaphylaxis with HPV vaccine, ADRAC and ADRU have employed the Brighton Collaboration criteria. However, this approach has not been applied uniformly when assessing ADRs to other vaccines and it is unlikely that most reporters would be familiar with or use the same criteria when assessing their patients' symptoms.

A major difficulty in assessing reactions to vaccines arises from the extensive variation in reporter's interpretation and description of symptoms. These problems appear to be particularly prevalent in reports of HPV vaccine since the program is very broad, involving numerous reporters of varying degrees of clinical experience and reporters are particularly motivated to detect and report reactions with this new vaccine. ADRAC was encouraged about the effectiveness and high participation rate of the HPV vaccine surveillance programs, as this was not typical with new medicines of any type. However, for the same reasons, some caution needed to be applied when reaction rates obtained in this situation are compared with reaction rates obtained in less structured environments or even across different jurisdictions.

Regardless of possible confounding due to factors associated with stimulating reporting and variations in interpretation of clinical signs and symptoms, ADRAC was satisfied that the absolute rate of ADRs reported with HPV vaccine was relatively low, that the safety profile of HPV vaccine did not differ grossly from that seen with other vaccines, and that there was a favourable benefit-to-risk ratio for HPV vaccine.

The Committee reviewed the safety measures already in place to manage risks with HPV vaccine, including the requirements for parental consent and post-vaccination monitoring and the availability of rescue medications and dedicated follow-up clinics. It was agreed these were appropriate

strategies to manage reactions reported to date with this vaccine and they should be observed by those involved in administering the vaccine. It was noted that many reports suggested rescue medication were being used in a preventative manner, suggesting a cautious approach was being taken by health care professionals. Given the target population and relatively limited experience with this new vaccine, ADRAC agreed this approach could be justified in certain circumstances.

ADRAC agreed the strategies in place to manage the risks of ADRs with HPV vaccine appeared to be effective. There was no evidence to suggest further action is warranted at this time; however, **expert advisory bodies such as ATAGI could be requested to comment on the adequacy of the currently recommended duration of the post-vaccination observation period of 15 minutes.** The Committee requested TGA continue to liaise closely with the relevant Federal, State and Territory authorities involved in administering and monitoring the HPV vaccine program, and that these bodies be provided with regular updates on the safety of the vaccine.