Gardasil Expert Panel

Report to the National Manager, Therapeutic Goods Administration on the safety and efficacy of Gardasil

February 2009

PART B Tables and Figures

Tables

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Figures

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The primary focus of the Panel was safety issues.

Specifically with regard to a possible association between Gardasil administration and demyelinating diseases, the Panel reviewed reports from the TGA's Adverse Drug Reactions

System (ADRS) database of the following clinical syndromes associated with demyelination occurring within six weeks of Gardasil administration:

Central nervous system demyelination	clinically definite multiple sclerosis (CDMS); clinically isolated syndromes (CIS: optic neuritis and transverse myelitis); and acute disseminated encephalomyelitis (ADEM).
Peripheral nervous system demyelination	Guillain Barré Syndrome.

The Panel also liaised with Australian neurologists specialising in the treatment of demyelinating diseases to ascertain whether there had been other, as yet unreported, Gardasil-associated cases, whilst noting that this approach has significant limitations. For example, the administration of Gardasil may not be a routinely sought exposure in neurological history-taking and, in addition, these inquiries relied on neurologist recall, so undetected cases could not be entirely excluded.

Given the likely under-reporting of adverse events and the fact that vaccination history may not be routinely sought by neurologists, the Panel recognised that the Australian case ascertainment was likely to be incomplete. As there is no active monitoring system in place that could identify cases in a systematic way from the vaccine-targeted population as they arise, several indirect indicators of the incidence or prevalence of demyelinating disease were examined to see if there were any upward trends following the introduction of the Gardasil immunisation program. The chosen markers were requests for MRI scans for detection of demyelinating disease and the *de novo* prescribing of specific drugs used in the treatment of these conditions. In addition, as the background incidence of autoimmune neurological disorders is relatively low, an examination of new onset Type 1 diabetes mellitus, a relatively common autoimmune disease, was performed to increase the chance of detecting any evidence of Gardasil triggering autoimmune disease.

Findings

General safety

Safety data provided in updated clinical trial reports and from extensive post marketing surveillance show that Gardasil is generally well tolerated with most reported events being procedural complications, administration site reactions such as soreness, swelling, redness, and systemic events such as headache, nausea, rash and dizziness. The experience from post marketing exposure is generally consistent with that seen throughout the developmental clinical trials.

Demyelinating disorders

The Panel identified a total of ten cases of central nervous system demyelination that occurred in Australia in females aged 16 years to 26 years within six weeks of vaccination with Gardasil. Nine of these cases were identified from the TGA's spontaneous adverse reaction reporting system and one case was identified through liaison with treating specialists. Six of the cases were reported from NSW. Five of the reports were cases of multiple sclerosis referred to two Sydney neurologists with a specific interest in the disease

and these cases were the subject of an article published in the MS Journal[a]. The authors suggested the cases were noteworthy because they considered them to be unusual presentations of multiple sclerosis occurring soon after vaccination. However, following review of these cases, including discussion with the treating specialist(s), the Panel's neurologists concluded that the clinical presentations and subsequent course of disease in these five cases did not appear particularly unusual and that the likelihood of being able to discern a role of vaccination on the basis of specific clinical presentations was very low.

Importantly, of the ten cases of CNS demyelination reported in Australia, six were reports of new onset disease and four were reports of exacerbation of existing disease (either relapse of CDMS or CIS developing into CDMS). A single case of peripheral demyelination (Guillain Barré Syndrome) was also identified from the TGA's ADRS database.

Using the incidence of new demyelinating events in women 18-27 years from the Ausimmune study[b] Newcastle site, and an estimated 130,000-139,000 second Gardasil doses administered to women in this age group in NSW in the second half of 2007, the point estimate for the expected number of cases of demyelinating disease identified in women in this age group was 4.1 with a 95% CI of 1.9 to 7.8. The conclusion of the Panel's epidemiological analysis was that if all six reported cases represented complete ascertainment in NSW, the four cases that occurred in women aged 18-27 years would be within the expected range of demyelinating disease in unimmunised women in that age group in NSW over that time period.

Additional analyses of data for indirect indicators of the incidence or prevalence of demyelinating disease, although limited, did not suggest any major change in the occurrence of demyelinating illness among females aged 12-27 years, the vaccine target population, since the introduction of the vaccination program. However, changes of a lower magnitude would still be important to identify and may not be detected by these available systems.

The Panel also noted (and was reassured by) the outcomes of post marketing surveillance activities for Gardasil in the USA, where more than 20 million doses of Gardasil had been distributed to 31 August 2008. The available U.S. data did not support a causal relationship with the demyelinating disorders Guillain Barré Syndrome and transverse myelitis. In particular, two major pieces of work have been undertaken and reported recently to the CDC's Advisory Committee on Immunization Practices (ACIP):

- cases of Guillain Barré Syndrome and transverse myelitis identified from the Vaccine Adverse Event Reporting System (VAERS) database were reviewed and thirteen cases of Guillain Barré Syndrome reported to VAERS were confirmed. Of these, only five occurred between 4 and 42 days after vaccination (the CDC's window of biological plausibility) among persons who solely received Gardasil. Similarly, eight cases of transverse myelitis were confirmed and of these only two occurred between 4 and 42 days post vaccination (all cases having received Gardasil alone); and
- a preliminary analysis of a Rapid Cycle Analysis (RCA) Study, undertaken using data captured between August 20 2006 and July 20 2008 at seven sites participating in the

[a] Sutton I, Lahoria R, Tan I-K et al. CNS Demyelination and Quadrivalent HPV Vaccination. Multiple Sclerosis Journal. *Multiple Sclerosis* 2008; 1-4.

[b] The Ausimmune Study is a case-control study involving approximately 1000 people across Brisbane city, the Newcastle region, the Western Districts of Victoria and Tasmania, intended to examine how environmental factors influence immune diseases and how immune disorders vary by latitude across Australia.

CDC's Vaccine Safety Datalink (VSD) - representing active surveillance of 259,986 doses in females aged 9 to 17 years and 117,974 doses in females aged 18 to 26 years (total of 377,960 doses of Gardasil) – found no cases of Guillain Barré Syndrome, the only demyelinating condition investigated, in patients who received the vaccine in either age group.

Other potential safety issues

In view of the concern about autoimmune neurological events, the TGA's ADRS database was searched for chronic diseases of possible autoimmune aetiology in association with Gardasil vaccination. The search identified eleven original reports of new onset diseases of possible autoimmune aetiology and two reports of exacerbations of existing disorders. The new onset diseases included guttate psoriasis (3 cases), alopecia (2 cases) and rheumatoid arthritis, polyarthritis, antiphospholipid syndrome, goitre, lymphocytic hypophysitis and coeliac disease (all single cases). Although based on low case numbers, the event rate appears to be no higher than the expected background rate in this age group.

The Panel also undertook specific reviews of reports of anaphylaxis/hypersensitivity, pancreatitis, seizures (and associated syncope) and vulvovaginal reactions as these types of reactions had been identified and discussed by the ADRAC. A number of these issues have been assessed concurrently by the U.S. CDC as part of its analysis of data generated through VAERS (specifically syncope) and the VSD RCA Study (specifically seizures, syncope, anaphylaxis and 'other allergic reactions'). The value of the U.S.-based data is that they provide larger numbers of reports and greater exposure than would have been available from the Australian experience alone. Preliminary analysis from the VSD RCA Study of event rates for seizures, syncope and 'other allergic reactions' found no statistically significant differences in these outcomes in Gardasil recipients compared with controls.

Anaphylaxis

The occurrence of hypersensitivity reactions such as anaphylactic/ anaphylactoid reactions, bronchospasm and urticaria has received attention both in Australia and internationally. In Australia thirteen cases of anaphylaxis that conformed to the Brighton Collaboration case definition were reported to ADRAC by 31 August 2008. This gives a rate of 2.88 cases per million doses distributed, which is consistent with the published rates for other vaccines administered to children and adolescents of 1.53 cases per million doses (95% CI: 0.04 to 8.52)[c], and the rate of 0 cases per million doses (95% CI: 0.00 to 9.76) from the U.S.-based VSD RCA study (also using the Brighton Collaboration case definition). Furthermore, the cases reported in Australia have not been at the severe (life-threatening, shock-type) end of the anaphylactic clinical spectrum. The Panel also reviewed the combined Australian experience, reported from three jurisdictional school-based HPV vaccination programs and concluded that hypersensitivity and, in particular, anaphylaxis is rare. It is important that immunisation providers remain aware of the possibility of hypersensitivity. In this regard, appropriate safety measures are already in place to manage risks of anaphylaxis with Gardasil, including the requirements for parental consent, the use of post-vaccination monitoring, the availability of rescue medications and the existence of dedicated follow-up clinics.

[c] Bohlke K, Davis RL, Marcy SM, et al. Vaccine Safety Datalink Team. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; **112(4)**: 815-20.

Pancreatitis

Seven reports consistent with a diagnosis of pancreatitis were identified from the TGA's ADRS database. Most reports (five) were of single, acute episodes of pancreatitis with time to onset ranging from 1 to 141 days after Gardasil injection, with no apparent clustering of the dose number or time to onset across the cases. Furthermore, many of the reports contained incomplete investigative information to categorically rule out other causes. However, whilst acute pancreatitis is a relatively common disease, it is not a common presentation in young women or non-drinkers. Thus, reports of pancreatitis should continue to be monitored closely and followed up to the fullest extent possible by the TGA.

Vulvovaginal reactions

The TGA has also received thirteen reports of vulvovaginal reactions, some of which can be explained by other factors, such as pre-existing HPV infection and local trauma. In the remaining cases, the diagnostic work up appeared incomplete. None of the cases included screening for Epstein-Barr virus infection, which is prevalent in adolescents and can manifest with symptoms of vulval/vaginal ulceration. Furthermore, it is important to recognise that even after complete diagnostic work up, 25% of patients with genital ulcers do not have a laboratory confirmed diagnosis[d]. Overall, at this point, there is no clear evidence of an association between Gardasil and vulvovaginal reactions or ulceration.

Overall, at present, for each of these potential issues there is no firm evidence of a causal relationship with the administration of Gardasil but the occurrence of such events must remain under careful scrutiny by the sponsor and regulatory authorities.

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Assessment of Merck Sharp and Dohme's Risk Management Plan (RMP) for Gardasil

It is clear that data limitations identified at the time of original marketing approval are generally being addressed by the sponsor through ongoing clinical studies and current and planned post marketing epidemiological studies. Issues identified from both ongoing clinical trials and post marketing surveillance have been factored into the sponsor's updated Risk Management Plan, which contains a detailed Action Plan for each safety concern.

On the whole, the Panel considers the actions proposed by MSD in its RMP to be necessary. In particular, the Panel noted MSD's proposal to conduct a series of prospective case control studies for the surveillance of Guillain Barré Syndrome and conditions of special interest such as systemic lupus erythematosis, rheumatoid arthritis, acute disseminated encephalomyelitis and CNS demyelination/multiple sclerosis using a French database. The status of the proposal at this stage is exploratory only, the protocol is not yet finalised and the number of cases of multiple sclerosis that can be recruited within 3 years is uncertain. Also, the time lag between a first demyelinating event and the diagnosis of multiple sclerosis can be several years. Therefore, the Panel believes this proposal may not be adequate. Australia is well placed to investigate a possible association between Gardasil and demyelinating events as:

- a large scale vaccination program has already been underway in Australia for 18 months;
- there is recent experience in investigating the epidemiology of demyelinating diseases at the population level; and
- there is potential to build on this previous platform.

Conclusions

The TGA registered Gardasil on the basis of a favourable benefit-risk balance. The evidence currently available from ongoing clinical trials and intensive global post marketing surveillance activities does not suggest that the safety profile of the product has altered significantly. The Panel has therefore concluded that no additional regulatory action is required at this stage.

Given that more than 4.5 million doses have been distributed in Australia to 31 October 2008 and about 10 million individuals have been vaccinated worldwide, it is to be expected that a number of serious illnesses, including demyelinating disease, will occur in close proximity to the time of vaccination, purely by chance. A review of previous studies of neurological outcomes following other vaccines (notably hepatitis B vaccine) showed that most concerns arising in relation to demyelinating disorders have been discounted after subsequent detailed scientific investigation. To date, the only setting where the onset or exacerbation of a neurological disease has been identified as a possible, but very rare, adverse event after vaccination is Guillain Barré Syndrome following administration of the now obsolete swine influenza vaccine.

Based on the currently available evidence, the incidence of demyelinating disorders amongst recipients of Gardasil vaccine is not demonstrably higher than would be expected by chance. However, this finding is limited by the uncertainty of case ascertainment. This is in the context of the large Gardasil population program targeting a group (young adult women), among whom the incidence of demyelinating disorders is well known to rise sharply between the ages of 16 and 27 years.

Nevertheless in view of the serious nature of demyelinating events this issue requires further evaluation and ongoing monitoring. Specifically, the Panel considers that comprehensive active surveillance is required to achieve more complete and timely case ascertainment and to assess the cases of demyelination following Gardasil vaccination in a population based sample. Further epidemiological investigation may also be needed, but this issue should be reconsidered pending the results of the recommended active surveillance.

Recommendations

The Panel recommends that:

1. All reports of an association between Gardasil and demyelinating disorders continue to be monitored via the current spontaneous reporting mechanism to the TGA's Adverse Drug Reactions System database.

2. Enhanced active surveillance is required to identify all possible cases of demyelinating disorders in a defined at-risk population, as it is well known that reporting through the passive surveillance systems is usually incomplete. This should include an active audit of cases of demyelinating events in a defined population, commencing in 2009, with results reviewed at least quarterly. Such surveillance would generate more accurate information about the incidence of demyelinating disorders and facilitate investigation of cases following Gardasil vaccination. It is recommended that the Panel be asked to endorse the final design and protocol for the surveillance activity.

3. If enhanced surveillance identifies a reason for concern, additional studies, such as case-control studies, would be warranted to further evaluate the validity and statistical significance of the observed association between Gardasil vaccine and the onset or exacerbation of demyelinating disorders. It is recommended that the Panel be asked to endorse the final design and protocol of any such study.

4. Any future large scale vaccination programs, especially those involving new vaccines, should have appropriate risk management strategies, including active surveillance mechanisms, established before commencement.

Abbreviations

ACIP	Advisory Committee on Immunization Practices, CDC
ADEC	Australian Drug Evaluation Committee
ADEM	Acute Disseminated Encephalomyelitis
ADRAC	Adverse Drug Reactions Advisory Committee
ADRS	Adverse Drug Reactions System, TGA
AIHW	Australian Institute of Health and Welfare
AIS	Adenocarcinoma in situ
CDC	Centers for Disease Control and Prevention, United States of America
CDMS	Clinically definite multiple sclerosis
CIN	Cervical intraepithelial neoplasia
CIS	Clinically isolated syndrome
CISA	Clinical Immunization Safety Assessment Network (U.S.A)
CNS	Central Nervous System
EMEA	European Medicines Agency
FDA	Food and Drug Administration, United States of America
FDE	First demyelinating event
GBS	Guillain Barré Syndrome
GLP	Good Laboratory Practice
HPV	Human Papillomavirus
MBS	Medical Benefits Schedule
MCO	Managed Care Organisation
MS	Multiple sclerosis
MSD	Merck, Sharp and Dohme Australia Pty Ltd
MRI	Magnetic resonance imaging
NDSS	National Diabetes Services Scheme
OMSM	Office of Medicines Safety Monitoring, TGA
PBS	Pharmaceutical Benefits Schedule
PSUR	Periodic Safety Update Report
RCA	Rapid Cycle Analysis
RMP	Risk Management Plan
SOC	System Organ Class
TGA	Therapeutic Goods Administration
VAERS	Vaccine Adverse Event Reporting System, FDA
VaIN	Vaginal intraepithelial neoplasia
VSD	Vaccine Safety Datalink, U.S. CDC
VIN	Vulvar intraepithelial neoplasia
WAES	Worldwide Adverse Experience System, an MSD database
WHO	World Health Organisation

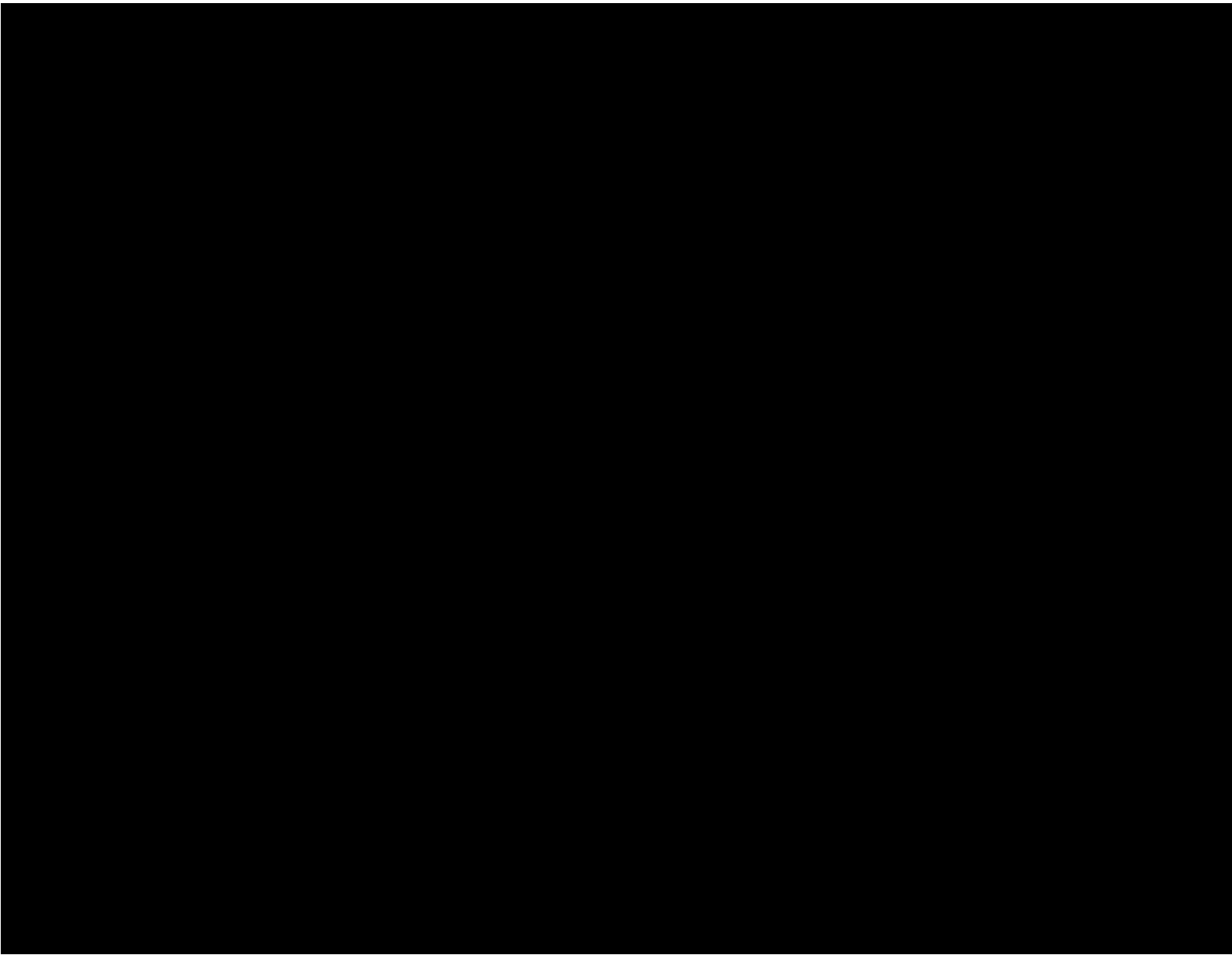
Part A. The Assessment Report

1. Establishment of the Gardasil Expert Panel

The Gardasil Expert Panel (the Panel) was established in August 2008 for the purposes of undertaking a medical and scientific evaluation of the human papilloma virus vaccine, Gardasil in order to provide advice to the TGA on whether the safety profile of Gardasil is acceptable when weighed against its efficacy.

The Panel was specifically requested to consider whether a small number of reports of demyelinating neurological disorders following immunisation that had been received by the TGA represented a safety signal that required further investigation, in which case the Panel was also asked to consider and advise on the elucidation of a mechanism through which the effect may be mediated and any actions through which the risk of occurrence could be minimised.

Where the Panel considered the reports were of uncertain significance, it was requested to provide advice on the adequacy of existing pharmacovigilance activities (as reflected in the sponsor's Risk Management Plan) to address that uncertainty, to recommend any additional pharmacovigilance activities that may be instituted to further characterise the safety profile of Gardasil, and to identify any risk minimisation strategies required in the interim.



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Clinical efficacy

With respect to clinical efficacy data, there were a total of twelve randomised clinical trials, seven of which used Gardasil as the trial vaccine. Four randomised double blind studies of Gardasil were considered pivotal to the demonstration of efficacy (Protocols 005, 007, 013 and 015). Combined, these studies evaluated 20,845 women aged 16 to 26 years who received either Gardasil or placebo in a standard three dose regimen (0, 2 and 6 months). Analyses of the combined trials were prospectively planned and included the use of similar

[1] Data provided by the Immunisation Programs Section, Targeted Prevention Programs Branch, Population Health Division, Commonwealth Department of Health and Ageing.

study entry criteria. The primary endpoint was considered by the TGA's clinical evaluator to be HPV 16/18-related CIN2/3 and AIS[2].

The key prophylactic efficacy findings are shown in Table One (page 49) which has been reproduced from the then approved Product Information for Gardasil. The results presented are for the per-protocol efficacy (PPE) population which comprised subjects who received all three doses, had no major deviations from study protocol and were naïve to the relevant HPV types prior to dose 1 through 1 month post dose 3. Of particular note, the efficacy of Gardasil in preventing HPV 16- and 18-related CIN 2/3 or AIS was better than 92.9% in the pooled analysis, and for HPV 6-11, 16-, and 18-related external genital disease and vaginal disease the efficacy was better than 95% in the pooled analysis.

Subjects with HPV infection at the time of enrolment did not show any statistically significant reduction in CIN or AIS compared to placebo, with an estimated efficacy of 27% (95%CI <0.0 – 47.0).

The evidence available at the time of marketing supported the conclusion that:

- prophylactic use of Gardasil with a 3 dose regimen at 0, 2 and 6 months was highly effective in 18 to 26 year old women at reducing the risk of them developing:
  - new and persistent HPV 6, 11, 16 and 18 infections;
  - HPV 16 and/or 18 related CIN 2/3 and /or AIS or HPV 6, 11, 16, 18 related VIN2/3 and/or VaIN 2/3; and
  - HPV types 6, 11, 16 or 18 CIN 1, genital warts, perianal warts, VIN 1, VaIN 1 (noting that these conditions are not predictive of cervical, vulval or vaginal cancer);
- vaccination with Gardasil has no therapeutic efficacy in women who are infected with a vaccine HPV type (i.e. 6, 11, 16 or 18) at the time of vaccination; and
- Gardasil vaccine administered as a three dose schedule is immunogenic and produces elevated titres of anti-HPV antibodies compared to those observed in subjects receiving placebo and those who have naturally acquired infection.

However, limitations in the dataset were also noted. The ability of the vaccine, when administered to children and adolescents aged less than 16 years to prevent HPV infection in those subjects when they become sexually active was not studied[3]. Furthermore there were no clinical disease efficacy data in males. A phase III adolescent-adult bridging study demonstrated the immunogenicity (as measured by anti-HPV antibody titres post dose 3) in 10 to 15 year old female and male subjects was as least as strong as that in 16 to 23 year old females who were HPV naïve at baseline. Another ongoing study (Protocol 018) showed an antibody response in 9 to 15 year old boys equivalent to that generated in 9 to 15 year old girls and that 98% of boys and girls had detectable antibodies. These results were used to support the bridging of efficacy in 16 to 26 year old females to 10 to 15 year old female and

[2] CIN = Cervical intraepithelial neoplasia, AIS = Adenocarcinoma in situ, VIN = Vulvar intraepithelial neoplasia and VaIN = Vaginal intraepithelial neoplasia. Although the ideal endpoint for HPV vaccine efficacy would be the development of invasive cervical and anogenital cancer, such endpoints were not feasible because lengthy and large trials would be required because of time for cancer to develop and rarity of cancer and, more importantly, because it would be unethical to allow women to develop cervical cancer given that the condition can be prevented and treated. CIN 2 or 3 or AIS precede invasive cancer and can be used as surrogate markers for the development of invasive cancers (in line with recommendations by expert panels of the FDA and WHO).

[3] This would have required studies with a very long follow up period. When efficacy studies have been considered unfeasible for other vaccines, the usual method has been to demonstrate there is a correlation between antibody titres and protection against infection. However, for Gardasil no correlation had been made between anti-HPV antibodies and vaccine efficacy.

male subjects and formed the basis of the approval of Gardasil for use in these age groups. At the time of marketing approval it was noted by the TGA that the persistence of antibody response had only been studied to 2 years and this concern was reflected in requirements for the future submission of data by MSD in the conditions placed on the marketing approval of Gardasil (see Section 2.2, page 5).

Clinical Safety

The safety data available at the time of registration of Gardasil in Australia were generated entirely from the premarket clinical trial program. There were no post marketing surveillance data as Gardasil had not yet been released for marketing anywhere in the world.

The clinical safety data for Gardasil were generated from 11,778 patients and compared with data from 9,686 patients who received placebo (some with and some without aluminium adjuvant). Safety was assessed using two methods:

- a Vaccine Report Card (VRC)-aided surveillance method, in which subjects (or guardians) recorded their daily temperature and the occurrence and severity of non-serious and serious events for 5 days and injection site reactions and systemic events for 15 days, with the study investigator being responsible for assigning causality according to the standard five point scale; and
- a general surveillance method – in which subjects spontaneously reported adverse events at visits throughout each study (in Protocol 015 subjects were prompted at each visit for serious adverse events).

In general, the rates of injection site-related events were higher in the Gardasil group compared to the placebo group. In the Gardasil group 63.8% of subjects experienced one or more injection site adverse experiences in days 1 to 5 post injection compared to 33.6% of the placebo (non aluminium) group and 60.6% of the placebo (aluminium) group. These results suggested the adjuvant is the agent responsible for injection site reactions. However, injection site reactions tended to increase in the Gardasil group with subsequent injections, suggesting the mechanism of injection site reactions with subsequent doses may relate to the development of an immune reaction to vaccine antigens.

Systemic adverse events were observed in 59% of Gardasil recipients compared to 60% of the placebo group, with comparable severity ratings. The most common events among the Gardasil recipients were headache (26%), pyrexia > 37.8^0C (12.9%) and nausea (6.1%). A total of 8 deaths were reported in the Gardasil group and 6 in the placebo group, mostly due to trauma, other medication overdose and pulmonary embolus (most likely related to oral contraceptive use). Serious vaccine-related adverse events were observed in 5/11,778 Gardasil recipients and 2/9,686 placebo recipients[4].

The main concern was the relatively limited number of subjects in the age range that would be targeted in mass vaccination programs and the limited duration of follow up. For example only 2,736 subjects aged <15 years were included in the safety assessment, compared to 8,383 adults (age >18 years). The relatively low numbers limited the ability to detect rare and/or delayed adverse reactions, particularly in sub populations.

[4] The types of serious vaccine-related events were (noting that a subject could experience more than one event) bronchospasm (day 1), headache (day 1), hypertension (day 1), injection site movement impairment (day 1), gastroenteritis (day 5) and vaginal haemorrhage (day 26) for Gardasil, and pyrexia (day 1), chills (day 1), hypersensitivity (day 3) for placebo.

2.2 Conditions of Gardasil registration and expectations of submission of additional efficacy and safety data generated during marketing

Conditions of registration were imposed by the TGA at the time of marketing approval. In addition to the standard conditions applied to all approved therapeutic goods, certain specific conditions, focussed on further elucidating efficacy and safety information for Gardasil, required MDS to provide the following information to the TGA:

- the final Clinical Study Reports for Protocols 013 and 015 when completed;
- long-term follow up of subjects enrolled in Protocol 015 from the cancer registries in four countries in the Nordic region (Sweden, Norway, Iceland and Denmark);
- data on the duration of immunity generated from the extension of Protocol 018-06;
- long term safety data from protocol 018-05;
- a report of the efficacy studies of Gardasil in 16 to 26 year old males that was ongoing at the time of approval; and
- annual reports and a final summary report of the U.S. pregnancy registry established by MSD.

These conditions closely mirror the postmarketing commitments given by MSD at the time of the granting of marketing approval in the USA. An additional commitment in the USA was that MSD would conduct a short term safety surveillance study in a US Managed Care Organisation (MCO), involving 44,000 vaccinated subjects who would be followed for 60 days (to assess short term safety such as emergency room visits, hospitalisation and deaths) and for 6 months following the completion of vaccination (to monitor for new autoimmune disorders, rheumatologic conditions and thyroiditis). It was expected that patient accrual would be completed by June 30 2009, with an interim study report to be submitted by September 30 2009.

The status of these commitments/requirements at the time of drafting this report are shown in Table Two (page 50). It can be appreciated that updated immunogenicity data and safety data, generally, as well as final study reports from protocols 013 and 015 have been submitted to the TGA as part of applications for extensions of indication in 2007 and 2008.

2.3 Submission of data from ongoing clinical studies and post market experience in 2007 & 2008

2007

In May 2007 MSD submitted an application to extend the approved indications to include prophylaxis against HPV 31-, 33-, 52- and 58-related CIN grades 1, 2 or 3 and AIS. This indication was later withdrawn (in February 2008) following an adverse recommendation by the TGA Delegate. However, additional clinical data were submitted from protocols 007, 013 and 015 that served to update the prophylactic efficacy with respect to HPV 16 or HPV 18 related CIN and AIS etc, and to provide further support for the persistence of antibody response and evidence of immune memory attributable to the vaccine. The application also included additional safety data from the ongoing studies protocol 007-10, 013, 015 and 018 with data cut off June 2006 or October 2006. This information was used to update the approved product Information for Gardasil, which was finalised in March 2008.

Review of the updated results from protocols 007, 013 and 015 suggested that claims made in the original application with regard to prophylactic efficacy and immunogenicity were supported. Table Three (page 51) summarises the updated efficacy data available at that time. Three pivotal clinical trials (007, 013 and 015) continued after the data cut-off date for the original application. No new subjects were enrolled in any of the studies but endpoint data continued to accrue in the intervening period. It can be appreciated from a comparison of Tables One and Three that over time, as the number of cases of CIN, VIN and VaIN in the placebo control group increased while cases in the Gardasil group remained more or less the same, the point estimates for Gardasil prophylactic efficacy have become more precise, with the 95% CI intervals narrowing. There was no evidence to demonstrate that Gardasil was not as prophylactically efficacious as first thought.

One study 007-10 provided additional information on the persistence of anti-HPV antibodies and immunogenicity up to 5 years post initial immunisation. Sero-positivity rates at month 60 post immunisation among subjects who received three doses of Gardasil were 89.9% for HPV type 6, 91.1% for HPV type 11 and 98.8% for HPV type 16.

Fewer subjects remained anti-HPV 18 positive at 60 months compared to the other HPV types but anti-HPV sero-positivity remained above 64%. For all HPV types, the highest anti-HPV antibody levels were observed at month 7, declining to month 18 and then remaining steady through to month 60. Antigenic challenge with a dose of Gardasil was performed in 241 subjects at month 60. Strong anamnestic responses were observed. At one week following the challenge, 87.2%, 94.9%, 86.4% and 95.2% of subjects had anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 levels higher than those observed before the challenge.

There were no new trends or issues identified in the clinical trials with regard to the safety of Gardasil. The most common injection site events continued to be pain, swelling and erythema and the most common systemic events were headache, pyrexia and nausea.

The submission also included post market surveillance data accrued from experience with over 2 million doses distributed worldwide since the time of the first marketing approval. The TGA's evaluation included a review of Periodic Safety Update Reports (PSURs) through to 30 November 2007. At that time the TGA also reviewed information emanating from overseas regulatory agencies and from the ADRAC's review of emergent safety issues (see Section 4, page 9).

The most frequently reported adverse events were medical device complication (premature activation of the safety device and leakage from the syringe), inappropriate schedule of drug administration, injection site pain and syncope. The most frequently reported serious adverse event was convulsion (5 reports, including 2 after syncopal episodes) and grand mal convulsion (3 reports). As a result of this post marketing experience, a number of adverse events were added to the core safety information for Gardasil by MSD, including syncope, dizziness and Guillain Barré Syndrome (under nervous system disorders), nausea and vomiting (under gastrointestinal disorders), hypersensitivity reactions such as anaphylactic/anaphylactoid reactions, bronchospasm and urticaria (under immune system disorders) and lymphadenopathy (under blood and lymphatic system disorders). Of particular note, there was only a single report of anaphylaxis and no reports of CNS or peripheral nervous system demyelination (MS, leukoencephalomyelitis, optic neuritis, Guillain Barré

Syndrome), juvenile rheumatoid arthritis, autoimmune thyroiditis or grand mal convulsions as adverse events in the clinical trial program.

2008

In March 2008 MSD submitted an application to extend the indications of Gardasil to include use in women up to the age of 45 years. This application included a further 7 months data for protocols 013 and 015 as well as a new study in women aged 27 to 45 years (protocol 019). There were no new efficacy data for protocols 005 or 007. The TGA's evaluation is yet to be completed and it is expected the application will be referred to the Australian Drug Evaluation Committee (ADEC) for its expert review of the data submitted in support of the additional claims relating to women aged 27 to 45 years. Thus, the Panel has limited its review to the most up-to-date prophylactic efficacy and immunogenicity data respect to the current approved indications. The updated prophylactic efficacy in females is summarised in Table Four (page 52).

Once again, number of cases of CIN, VIN and VaIN in the placebo control group increased while cases in the Gardasil group remained more or less the same, such that the point estimates for Gardasil prophylactic efficacy have become more precise, with the 95% CI intervals narrowing. In subjects with evidence of current HPV infection with a vaccine HPV type (6, 11, 16 or 18), administration of Gardasil had no impact on the incidence of HPV 6-, 11-, 16- or 18-related CIN (any grade), AIS or external genital lesions caused by that particular type, confirming Gardasil has no therapeutic efficacy. However administration of Gardasil reduced the risk of acquiring CIN (any grade), AIS and external genital lesions caused by other vaccine HPV types to which they were naïve at day 1.

Updated immunogenicity data were available from studies 013 and 015, which included results from end-of-study visits at month 44, and study 018 (conducted in subjects aged 9 to 15 years) which included results from the month 18, month 24 and month 30 visits (original application included results only through month 7). Analyses of these data showed that anti-HPV mean geometric titres (GMT) at month 7 were highest among 9 to 17 year olds. The anti-HPV GMTs at month 7 among 18 to 26 year olds were only about half (52 to 62%) of the levels observed among 9 to 17 year olds. The rate of decline over the ensuing period was more pronounced in the younger age group, but the proportions of subjects who were anti-HPV seropositive at month 24 remained high and were comparable between the 9 to 17 year old and 18 to 26 year old age groups. Protocols 013 and 015 provided data on persistence of anti-HPV responses at end of study (i.e. up to 4 years post vaccination) in the 18 to 26 year age group. Anti-HPV GMTs reached their highest measured levels at month 7 and declined thereafter, but anti-HPV 6, 11, 16 and 18 GMTs at end of study were at or above the anti-HPV GMTs observed following natural infection.

There were no new safety signals arising from the updated clinical trial data. The most common new medical condition reported after Day1 was vaginal candidiasis in both the Gardasil (9.8%) and placebo (12.0%) groups. The number of deaths occurring throughout the clinical trial program had risen to 23 -15 (0.11%) in the Gardasil group and 8 (0.07%) in the placebo group. None of the deaths in either group were considered to be vaccine- or procedure-related. The most common injection site events continued to be pain, swelling and erythema and the most common systemic events were headache, pyrexia, nausea and nasopharyngitis. The most common serious adverse events were overdose (either of

vaccine/placebo or of non-study medicines), infections (urinary tract infections and viral illnesses) and complications of pregnancy.

An analysis of new medical conditions potentially indicative of an autoimmune phenomenon that occurred during the clinical trials was also presented. The conditions are shown in Table Five (page 53), which compares the Gardasil and placebo groups (shown in order of frequency of occurrence in the Gardasil group). Overall, the proportion of patients experiencing such new conditions was comparable between the two groups. Furthermore, in both groups the most common new condition potentially indicative of an autoimmune phenomenon was hypothyroidism, occurring at a rate of 0.3% in the Gardasil group and 0.5% in the placebo group. Of particular relevance to the Panel's brief in respect of demyelinating disorders, two cases of multiple sclerosis and two cases of optic neuritis have been reported with Gardasil and four cases of multiple sclerosis for placebo in the clinical trial program.

Detailed pregnancy data, including clinical trial data and the 2nd annual report on exposure during pregnancy from MSD's Pregnancy Register were also submitted to the TGA as part of the application. Table Six (page 54), which has been reproduced (with some adaptation) from the TGA's clinical evaluation report, summarises pregnancy outcomes from the Phase III clinical trial program (including protocol 019 conducted in women aged 26 to 45 years of age). The proportions of pregnancies resulting in live births and foetal loss were comparable between the two groups. A total of 70 congenital abnormalities were detected in the clinical trial program, with a slightly higher rate in the Gardasil group – 40 (2.8%) in subjects receiving Gardasil and 30 (2.1%) in the placebo group. The observed anomalies in the Gardasil group were quite diverse with regards to aetiology, timing of event during embryogenesis and organs affected. Overall it was considered that no signal had been detected to account for the slightly higher rate for the Gardasil group. Key findings from MSD's Pregnancy Register were:

- For the period 1 June 2006 through 31 May 2008 (i.e. the then entire period of product licensure globally), there had been 787 pregnancies prospectively enrolled, with 517 pregnancy outcomes;
- Of the 517 reports with known outcomes, 491 had a natural outcome and 26 had been terminated through elective abortion;
- Of the 491 with natural outcomes there had been 415 live births, 34 spontaneous abortions and 7 foetal deaths;
- The spontaneous abortion rate of 6.9% was considered to be lower than expected in the general population[5];
- The foetal mortality rate, defined as foetal death after 20 weeks gestation, of 1.5% was slightly higher than rates of 0.62 % to 1% reported for the general population[6]; and
- There were 10 reports of major congenital abnormality – 9 occurring in live births and 1 in an elective abortion. The observed rate of 2.2% was slightly lower than previously reported rates from the Metropolitan Atlanta Congenital Defects Program for the presence of major malformation at birth of 2.67%[7].

[5] Although the rates of spontaneous abortion depends on the manner in which pregnancy is detected, among clinically recognised pregnancies, the spontaneous abortion rate is 15%.
Scott JR. Early Pregnancy Loss. In: Scott JR, Di Saia PJ, Hammond CB, Spellacy WN eds 1999. Danforth's Obstetrics and Gynaecology. Philadelphia: Lippincott Williams & Wilkins.
[6] MacDorman MF, Munson ML, Kirmeyer S. Fetal and perinatal mortality, United States 2004. Natl Vital Stat Rep 2007; 56(3).
[7] Correa et al. Metropolitan Atlanta Congenital Defects Program, 40th anniversary edition surveillance rport. Birth Defects Research, Part A: Clinical and Molecular Teratology; 79(2): February 2007.

The number of reports with known outcomes data is still quite limited and it is not possible at this stage to draw definitive conclusions about the potential effect of Gardasil exposure during pregnancy.

3. Overview of Australian spontaneous adverse drug reaction reports for Gardasil

As at 31 October 2008 there had been a total of 1202 reports of suspected adverse reactions, with 3464 reaction terms for Gardasil sent to the TGA. Reports received by System Organ Class (SOC) are shown in Table Seven (page 55), which also includes commonly reported reaction terms.

Events most commonly reported by SOC have been General and administration site disorders (644), Nervous system disorders (616), Skin and subcutaneous tissue disorders (459) and Gastrointestinal disorders (349).

With respect to the types of reaction reported, the majority of cases are mild and common problems such as soreness, swelling, redness or other reactions at the injection site (mentioned in 255 reports; 21.2% of reports). Other commonly reported reactions have included headache (244; 20.2%), nausea (195; 16.2%), rash (193; 16.1%), dizziness (172; 14.3%), urticaria (107; 8.9%), malaise (100; 8.3%) and vomiting (94; 7.8%).

4. Specific safety issues arising from post marketing experience

4.1 Overview of Australian experience

Several specific issues have been identified and discussed by the Adverse Drug Reactions Advisory Committee (ADRAC) since the registration of Gardasil as follows:

July 2007 — Anaphylaxis and Gardasil: The ADRAC had been reviewing in detail all reports involving HPV vaccine that suggested a possible anaphylactic reaction. The ADRAC recommended that product literature for consumers and health professionals be reviewed to ensure adequate description of risks of anaphylaxis and requirements for monitoring and management of symptoms after vaccination.

Nov 2007 — The ADRAC Members noted three main groups of adverse reactions had been reported with Gardasil:

- Syncopal/conversion-type events;
- Unusual neurological symptoms including various types of aesthesia;
- Skin rash at various times following immunisation; and
- Level 1-3 Anaphylaxis according to Brighton Collaboration Criteria

Dec 2007 — Members discussed possible factors that may contribute to apparent differences in reported rates of anaphylaxis with Gardasil vaccine compared to other vaccines. This was in response to an observation that the reported rates

of anaphylactic reactions to HPV vaccines in NSW were disproportionately greater than in other areas and appeared to be in the order of 10-20 times greater than the rates reported for other vaccines. At that time it was noted there is no uniformly applied case definition for anaphylaxis – in particular, the ADRAC had been using the Brighton Collaboration definition[8] which was a more encompassing definition of anaphylaxis than used previously. Thus, it was felt it was difficult to directly compare current rates for Gardasil with historical vaccine-associated rates. The ADRAC was satisfied that the absolute risk of adverse drug reactions reported with Gardasil vaccine was relatively low, that the safety profile did not differ grossly from that seen with other vaccines, and that there was a favourable benefit-to-risk ratio for Gardasil vaccine. This issue was again discussed at the February 2008 meeting of the ADRAC, at which the NSW Health HPV Vaccination Program Adverse Events Review Panel interim report of cases of anaphylaxis following Gardasil vaccination in NSW was considered. It was noted that at that time there had been 11 reports of anaphylaxis and 97 reports of urticarial reactions in Australia following Gardasil. The estimated rate of anaphylaxis based on doses given in Australia was 3.2 per million. It was noted the rates for other vaccines given to children and adolescents range from 0 to 3.5 per million doses in international studies.

At the December 2007 meeting, the ADRAC also reviewed its first two cases of pancreatitis and suggested a watching brief should be maintained for pancreatitis and related reactions with HPV vaccine

April 2008 — The ADRAC reviewed several reports of vulvovaginal reactions following Gardasil vaccination. Expert option was sought from an adolescent gynaecologist on the likely background incidence of vulvovaginal lesions. Comments were that the average onset time was 24 hours post vaccination, and this time frame is short for a typical autoimmune response. It was noted that this reaction may be a flare up of an existing HPV infection

May 2008 — The ADRAC noted that in the period covered by that Meeting, HPV vaccine accounted for 10 of the 14 reports of convulsions or seizures reported for vaccines. This brought the total number of reports of convulsions/seizures with this vaccine to 31 (from a total of 891 reports; 3.5%). On review of the case line listing and copies of the originals of the 31 reports it was noted the majority of the reports described seizures associated with syncope, rather than true seizures associated with neurological disorder. It was agreed the reports did not suggest a cause for concern and further investigation was not warranted at that stage.

July 2008 — The ADRAC was asked to review, as a matter of priority, 5 recently received reports describing multiple sclerosis-like symptoms in association with Gardasil and further information from a previously reported case. The 5 new cases were from two neurologists from the metropolitan Sydney region with a specific interest in the disease, who subsequently published a paper in the

[8] Rüggeberg JU, Gold MS, Bayas J-M, Blum MD et al., Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; **25**: 5675-5684.

medical literature[9]. The ADRAC members agreed the reports of MS in HPV-vaccinated females were of great concern and action should be taken to quickly establish if there is a vaccine-associated link. The ADRAC considered that while there would be a background rate of MS in females of various age groups, it was not yet clear how these rates compared with rates in HPV vaccinated females. The CNS lesions described in some of the cases are not typical of vaccine-associated neurological lesions, and the ADRAC was unable to draw conclusions about causality on the basis of pathology. It was noted that neurological reactions have been associated with other vaccines and there are plausible underlying mechanisms. The ADRAC considered that while an association between MS and HPV vaccine is plausible, it was not proven on the basis of reports reviewed to that time. The Committee recommended that immediate action to more actively monitor cases of MS and other neurological reactions in HPV-vaccinated females could be taken by using existing vaccine safety monitoring programs and relevant specialist networks.

4.2 International experience

Both the US Food and Drug Administration and the European Medicines Agency (EMEA) have closely monitored the safety of Gardasil. To date, based on the outcomes of their respective reviews, both agencies consider that Gardasil continues to be safe and effective, and that its benefits continue to outweigh its risks. Neither regulatory authority has made any changes to the prescribing information for how the vaccine is used or to the vaccine's Precautions.

The Panel has particularly noted the extensive post marketing surveillance available from the USA via the Vaccine Adverse Event Reporting System (VAERS), operated by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), and the Vaccine Safety Datalink (VSD), which is a collaborative project between CDC and eight U.S. Managed Care Organisations to study patterns in reports detected by VAERS to assess causal relationships[10].

As of August 31, 2008, the number of doses of Gardasil distributed in the USA was 20,383,145. On 22 October 2008, the results of the following analyses of Gardasil post marketing safety data were presented to the CDC's Advisory Committee on Immunization Practices (ACIP):

- a review of Gardasil data in VAERS, using reports received between 30 June 2006 and 31 August 2008, with a detailed analysis of selected serious conditions of clinical interest – syncope, venous thromboembolism, Guillain Barré Syndrome, transverse myelitis and

[9] Sutton I, Lahoria R, Tan I-K et al. CNS Demyelination and Quadrivalent HPV Vaccination. Multiple Sclerosis Journal. *Multiple Sclerosis* 2008; 1-4.

[10] Across the eight MCOs in VSD, data are captured from 8.8 million members annually (3% of the US population). The active surveillance data generated through VSD are more robust in that they address many of the limitations of spontaneous reporting systems such as VAERS, which include risk of underreporting, stimulated reporting due to media attention, incomplete data and lack of denominator data. The MCOs are Group Health Cooperative, Northwest Kaiser Permanente, Northern California Kaiser Permanente, Southern California Kaiser Permanente, Kaiser Permanente Colorado, HealthPartners, Marshfield Clinic and Harvard Pilgrim.

deaths – representing passive surveillance of more than 20 million doses. The analysis was complemented by detailed expert clinical review of reports of Guillain Barré Syndrome and transverse myelitis by members of the Clinical Immunization Safety Assessment (CISA) Network; and

- the results from a preliminary analysis of a Gardasil Rapid Cycle Analysis (RCA) Study, using data captured for specific events of interest occurring between August 20 2006 and July 20 2008 at seven VSD sites – representing active surveillance of 377,960 doses of Gardasil[11].

4.2.1 VAERS data and related CISA network activities

On 3 October 2008, prior to its presentation to the ACIP, the CDC reviewed all VAERS reports received to 31 August 2008 using Brighton Collaboration case definitions for the events. 'Confirmed cases' were those that met the case definition, but this does not mean they were necessarily causally associated with the vaccination.

As of August 31, 2008, there had been 10,326 VAERS reports of adverse events following Gardasil vaccination. The most frequent events following Gardasil vaccination were found to be syncope (1,564; 15%), dizziness (1,469; 14%), nausea (959; 9%), injection site pain (818; 8%), headache (731; 7%), pyrexia (680; 7%) and rash (580; 6%). These events are consistent with the premarketing clinical trial data.

A total of 619 (6%) reports were of a serious event (defined by the U.S. Code of Federal Regulations as leading to hospitalization, death, permanent disability, life threatening illness, or certain other medical important conditions). Serious adverse events for the selected conditions of clinical interest were: syncope (n=119, of which 70 were U.S. reports), venous thromboembolism (n=65: 41 U.S. reports), deaths (n=31: 27 U.S), Guillain Barré Syndrome (n=52: all U.S.) and transverse myelitis (n=13: 10 U.S.).

Deaths

Of the 27 US reports of death, 17 were of 'confirmed cases', 3 cases were pending and 7 were unable to be followed up. Of the 17 confirmed cases, the time to death from vaccination was available in 16 reports, ranging from 2 to 7 days in 6 cases, 13 to 21 days in 5 cases, 22 to 62 days in 2 cases, 62 to 117 days in 2 cases, to 288 days in the remaining case. Among the 'confirmed cases' and those 'pending evaluation,' the clinical conditions which preceded or caused deaths, some of which developed following Gardasil vaccination and others which were reported in the medical histories for these cases, were[12]:

- Viral illnesses (n=3) - acute myocarditis, meningoencephalitis, influenza B viral sepsis;
- Pulmonary embolism (n=2);
- Cardiac events (n=2) - arrhythmia due to cardiomyopathy, probable cardiac arrhythmia;
- Diabetic ketoacidosis (n=1);
- Idiopathic seizure disorder and history of seizures (n=1);

[11] The presentations were viewed at www.cdc.gov/vaccines/recs/acip/slides-oct08.htm#hpv. Minutes of the ACIP meeting were also viewed at www.cdc.gov/vaccines/recs/acip/downloads/min-oct08.txt. Formal reports of these analyses are not available and, therefore, these two sources of information form the basis of the detailed summaries below. A brief summary of results of the preliminary analysis of the VSD RCA Study was also reported in: Bridget M. Kuehn. CDC Panel Reviews HPV Safety Data. *JAMA.* 2008; **300**(23): 2713-2714.

[12] Note: even though the number of confirmed and pending cases totalled 20, there are only 19 conditions listed here, reproduced from the CDC website.

- Atypical GBS vs juvenile amyotrophic lateral sclerosis (n=1);
- Drug overdose (n=2); and
- Unknown cause (n=3) and limited information for further evaluation (n=4).

There was no common pattern to the deaths that would suggest they were caused by the vaccine – in particular there was no clustering by age groups, onset intervals or dose number. In cases where autopsy, death certificate and medical records were available, the cause of death was explained by factors other than the vaccine[13].

Venous thromboembolic events

Of the 41 US reports reviewed only 18 were 'confirmed cases'. A further 6 were pending evaluation and the remaining 17 reports were either unable to followed up (n=8) or there was no case (n=9). Of the 18 confirmed cases, 14 were currently using hormonal contraception. Of these, 12 cases were using oral contraceptive pills and 2 cases were using Nuvaring (etonogestrel/ethinyl oestradiol vaginal ring). Some of these cases also had additional risk factors. In the remaining 4 cases, 3 had other risk factors (pregnancy; combination of obesity, smoking and truck driving; and a preceding long bus ride). There was only one 1 case with no reported risk factors.

Syncope

There were a total of 70 US reports of syncope as a serious adverse event. These were coded as 'syncope' or 'syncope vasovagal'. Of these, 38 occurred on the same day as the vaccination, with 37 requiring hospitalization. The most commonly associated symptoms included loss of consciousness, dizziness, headache, nausea, vomiting, fall, and head injury.

Demyelinating disorders - Guillain Barré Syndrome, transverse myelitis

Cases of Guillain Barré Syndrome and transverse myelitis identified through the VAERS database were specifically reviewed by the Clinical Immunization Safety Assessment (CISA) Network[14]. Transverse myelitis cases were reviewed by the Johns Hopkins University and cases of Guillain Barré Syndrome were reviewed by the Boston Medical Center. Medical records were obtained for confirmed cases and reviewed by CISA investigators and clinical expert neurologists. The proposed Brighton case definition was used for confirmation of Guillain Barré Syndrome cases and the theoretical window of biological plausibility for immune-mediated neurologic events was considered to be 4 to 42 days following vaccination, based on experience from the Swine Flu epidemic with Guillain Barré Syndrome (1976-1977).

Of the 52 reports (all U.S.) of Guillain Barré Syndrome after Gardasil immunisation to VAERS, 11 cases did not meet the Brighton case definition, 12 cases had insufficient

[13] The European Medicines Agency (EMEA) has also received reports of deaths in women who had previously received Gardasil, including two reports concerning the sudden and unexpected deaths of two young women in Austria and Germany. In both cases the cause of death could not be identified.

[14] CISA is a network of six academic centres with vaccine safety subject matter experts, established to provide selected clinical consultations and to investigate the pathophysiologic mechanisms and biological basis of adverse events following immunisation. The centres are Boston Medical Center, Columbia University Medical Center, John Hopkins University, Northern California Kaiser Permanente, Stanford University Medical Center and Vanderbilt University Medical Center.

information for classification, 15 cases were pending evaluation and 1 case experienced symptoms prior to vaccination. Thus, most of the reports of Guillain Barré Syndrome submitted to VAERS were not confirmed. Only about 50% of the cases had adequate medical records available for review. There were 13 'confirmed cases', broken down as follows: Brighton level 1 diagnostic certainty (n=5), Brighton level 2 (n=6), atypical GBS (n=1), and Miller Fisher Syndrome (n=1). In the medical record review of the 13 confirmed cases, 6 received Gardasil alone, 6 received Gardasil and meningococcal C vaccine (Menactra®) and 1 received Gardasil and other vaccines. All but one of the confirmed cases occurred in females 13-20 years of age, with the remaining case occurring in a 56 year old male. Details of dose number were available for 12 of the 13 confirmed cases - 9 received 1 dose and 3 received 2 doses. Time to onset of symptoms ranged from 1 to 144 days, with 9 cases occurring between 4 and 42 days after vaccination. Four of these 9 cases also received meningococcal C vaccine.

A total of 13 reports of transverse myelitis had been submitted to VAERS - 3 were reports of multiple sclerosis (1 U.S. case), 2 had insufficient information for evaluation, and 8 cases were transverse myelitis (7 of these being US cases and 1 from Australia). The 8 cases of transverse myelitis were reported in females aged 11 to 26 years who had received Gardasil alone. A review for confounding conditions revealed 2 cases with a preceding viral illness and 1 case with a history of allergies and family history of autoimmune diseases. Of the 8 cases, 2 occurred after the first dose and 6 occurred following the second dose of Gardasil. Time to onset of symptoms ranged from 1 to 150 days, with 3 cases occurring within 2 days of vaccination, 2 cases occurring between 4 and 42 days after vaccination (i.e. within the theoretical window of biologic plausibility) and 3 cases occurring more than 42 days after vaccination.

4.2.2 VSD Rapid Cycle Analysis (RCA) Study of Gardasil

This ongoing study is designed to identify potential associations between Gardasil and a pre-specified list of new onset adverse events in females ages 9-26 years (divided into two groups – youth (9-17yrs) and adult (18-26yrs)) across seven participating VSD sites. The outcomes being monitored include Guillain Barré Syndrome, seizures, syncope, appendicitis, stroke, venous thromboembolism, anaphylaxis, and 'other allergic reactions'. Importantly, diseases caused by central nervous system demyelination are not covered.

Adverse events are monitored among the exposed cohort, which are females 9-26 years of age receiving Gardasil, either alone or with another vaccine. The exposure windows, medical setting, and first occurrence of the outcome in a defined time period are shown in Table Eight (page 56), which has been reproduced from the CDC's presentation to ACIP. Each week the number of events of interest in the vaccinated cohort is evaluated and compared to the expected number of events based on a comparison group. The rates are analysed weekly with statistical adjustment for multiple looks. It is planned to continue the study until 350,000 doses are reached in the 9-17 year old age group (youths) and 150,000 doses are reached in the 18-26 year old age group (adults).

In the analysis presented to ACIP, event rates for Guillain Barré Syndrome, appendicitis, stroke and venous thromboembolism were compared with background rates in an historical comparison group comprising females aged 9-26 years from two sources – participating VSD

site or Health Care Utilization Project – using the Poisson Max SPRT[15]. The event rates for seizures, syncope and 'other allergic reactions' were compared with a concurrent comparison group using Flexible Exact Sequential Analysis[16]. For syncope and 'other allergic reactions' the comparison group comprised females in the same age group who had a vaccination visit during the same time as the exposed group, which was 34,917 for adults and 106,252 for youths. For the analysis of seizures, the comparison group comprised females in the same age group that presented for a preventative care visit, which was 211,878 for adults and 141,329 for youths. No formal comparison was undertaken for anaphylaxis because the primary ICD-9 code for anaphylaxis is non-specific and generates a lot of false positives. Instead, each anaphylaxis case identified in the automated data was validated through chart abstraction to calculate the incidence rate.

Table Nine (page 57), also reproduced, but with adaptation, from the CDC presentation to ACIP, summarises the preliminary results obtained from data generated through to July 2008. The total number of Gardasil doses administered to that time across the participating VSD sites was 259,986 doses to female youths aged 9-17 years and 117,974 doses to female adults aged 18-26 years. It can be appreciated from the table that, to date, no signal has been generated for either youths or adults, for any of the outcomes of interest. However, the following results were of some note:

- the observed number of stroke events amongst adults (n=3) exceeded the expected (n=1.58) and there is an elevated Relative Risk (RR) of 1.91. However, since the Log Likelihood Ratio (LRR) does not exceed the critical value (2.97), at this time the data do not show a statistically significant association between Gardasil and stroke;
- the number of venous thromboembolic events observed among youths (n=7) exceeded the expected number (n=3.57), resulting in an RR of 1.96. However, once again the LRR did not exceed the critical value (3.25). During its presentation to ACIP, the CDC noted this outcome continued to be monitored very closely in the study despite the lack of a signal having been generated, with detailed review of the medical charts of all exposed and unexposed cases and, where necessary, collection of additional information such as hormonal therapy and other risk factors; and
- there were higher numbers of exposed (to Gardasil) cases than unexposed (to Gardasil) cases for syncope and 'other allergic reactions' in both the adult and youth groups. However, factoring in the number of vaccination visits gave RRs <1, with the exception of 'other allergic reaction' in the adult group. By way of explanation, unexposed cases are those adverse events that occur in a concurrent comparison group and the comparison visit for these outcomes was a vaccination visit. The number of vaccination visits in the comparison group for adults was 34,917 (compared to 117,974 Gardasil visits) and the number in the youth group was 106,252 (compared to 259,986 Gardasil visits). For example, for syncope there were 129 events that occurred among those adult females who received 117,974 doses of HPV vaccine compared to 57 events that occurred in the 34,917 vaccination comparison visits, giving a relative risk of 0.54. In the case of 'other allergic reactions' in the adult group, although the RR was 1.45, the binomial test p value

[15] The Poisson Maximum Sequential Probability Ratio Test (Poisson Max SPRT) analysis method is used for the relatively more rare adverse events in which the observed number of events is compared to an expected number from a background rate using historical data. Using this type of sequential analysis an association, or signal, is detected if the log likelihood ratio (LLR) exceeds the established critical value.

[16] In the Flexible Exact Sequential Analysis method, a weekly threshold p-value is established to account for the continuous monitoring. The p-value is generated for that week's test. If that p-value is less than the threshold, an association or signal is detected.

(0.26) exceeded the threshold p value (0.02) meaning there was no statistically significant association.

In view of the attention Gardasil had been receiving in the US over reports of syncope (see also the VAERS results), the CDC undertook an additional logistic regression analysis (with age and secular trend adjustment) that compared syncope rates following Gardasil with concurrent vaccination rates and found no excess risk among the youth or adult groups or for the groups combined (Table Ten, page 58). Furthermore, the secular trends for post-vaccination syncope following Td, Tdap, meningococcal C and varicella vaccines from 1996 to June 29, 2008 were examined and found to be increasing over time.

With respect to anaphylaxis, eight anaphylaxis events were identified among youths in the exposed group and nine events among those in the comparison group. In the adult group, seven events were identified among those who received vaccine and two who did not. Following detailed review of the records and charts of each of these potential cases, none of the codes were true anaphylaxis cases and none of these cases was vaccine-related. Consequently, the rate of anaphylaxis following Gardasil vaccination was 0 cases per million doses (95% CI: 0.00 - 9.76) which was considered to be consistent with the published background rate of 1.53 cases per million doses (95% CI: 0.04 - 8.52)[17].

4.2.3 Overall conclusions from US data analyses

The Panel has not reviewed the primary data from the VAERS and VSD RAC study but considers the results and conclusions from these analyses as presented to the ACIP to be reassuring. It particularly noted the CDC's view that the available data from U.S. surveillance does not support a causal relationship with Guillain Barré Syndrome and transverse myelitis. It also noted the finding that there had been no confirmed reports of anaphylaxis within the VSD.

The Panel noted the absence of a statistically significant risk for any of the pre-specified adverse events following vaccination in either the 9-17 year old age group or the 18-26 year age group in the RAC study but also recognises the limited power at this time to categorically rule out a true risk for rarer diseases. As an example, for Guillain Barré Syndrome, the CDC advised the ACIP that based on the observation of no cases per 420,000 doses (to the time of reporting to ACIP on 22 October 2008) they were unable to rule out a RR of less than 5. The Panel noted that the CDC plans to continue monitoring outcomes until the upper limits are reached or until the dose limit specified in this design of this study is reached. Even after the formal rapid cycle is completed, the CDC plans to continue monitoring the more rare adverse events such as Guillain Barré Syndrome, venous thromboembolism and stroke.

4.3 Australian reports of anaphylaxis

As at 31 October 2008, the TGA had received thirteen reports of anaphylaxis. These cases are summarised in Table Eleven (page 58). Nine of the reports have originated in NSW, two in WA and one each in Victoria and Queensland. Four of these occurred after the first dose of Gardasil, three with second dose; one after the third dose and no information on dose

[17] Bohlke K, Davis RL, Marcy SM, et al. Vaccine Safety Datalink Team. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; **112(4)**: 815-20.

number was given in the other five. All but one case was reviewed at hospital and all but one was administered adrenaline. Nine cases were stated to have fully recovered at time of reporting.

All reports of suspected anaphylaxis have been reviewed by the ADRAC and a level of certainty of diagnosis assigned using criteria established by the Brighton Collaboration. The Panel noted both the existing expertise and experience within the ADRAC for assessing anaphylaxis and allergic-type reactions and the ADRAC's extensive deliberations over the cases reported to the TGA to date. Thus, it was not considered necessary that the Panel should review the identification and classification of the cases.

The Panel also noted that a major difficulty in assessing reactions to vaccines arises from the extensive variation in reporters' interpretation and description of symptoms. The ADRAC has employed the Brighton Collaboration criteria in an attempt to provide a consistent and standard approach to identifying reports of anaphylaxis with Gardasil. However, the Brighton criteria for anaphylaxis are much more inclusive than previously applied criteria, such that more suspected cases would be captured than had previously been the case with other vaccines, meaning direct comparisons with historical vaccine-associated rates of anaphylaxis must be undertaken with caution.

Many of the cases of anaphylaxis have in fact not been the acute, life-threatening, multi-organ, anaphylactic shock-type reaction that is traditionally associated with the term anaphylaxis, but in the context of the Brighton classification and more recent understanding in fact probably represents just the extreme end of the severity spectrum. Furthermore, none of the cases have been assessed as level 1 certainty of diagnosis. Based on current Australian distribution figures, the estimated rate for anaphylaxis is 2.88 per million doses of Gardasil distributed and globally the rate of anaphylaxis with Gardasil is 1.6 per million doses distributed[18]. However, rates in specific age sub-groups and in the school-delivered campaign differ from this overall rate due either to real age-specific differences, varying case ascertainment or both.

An underlying concern is whether Gardasil is more allergenic than other vaccines. The "clustering" of reports from NSW could be due to local factors, e.g. reporters with varying degrees of clinical experience could be highly motivated to detect and report reactions with a new vaccine, rather than due to an inherently high allergenicity of the vaccine. However, the Panel notes the NSW data comparing notification of anaphylaxis in the school campaign with Meningococcal C conjugate vaccines in a similar age group. These data indicate that reporting rates were substantially higher in a context which would reduce but not eliminate recognition and reporting issues. In addition, the Panel reviewed the distribution of cases of urticaria reported to the TGA to see if there was a similar pattern. In particular, if there were higher rates of urticaria than observed historically with other vaccines, especially if there was a more even distribution across jurisdictions, it could lend some credibility to Gardasil being more allergenic. Reports of urticaria received by the TGA are presented by jurisdiction in Table Twelve (page 59) and appear to be relatively more evenly distributed across the jurisdictions.

A total of 110 reports with the reaction term urticaria were identified as having been reported to 31 October 2008. Three of these were found to be duplicates of other reports, leaving 107

[18] MSD Risk Management Plan 18 July 2008, page 41 (based on figures to 29 February 2008).

actual reactions across Australia. Sources of reports were state and territory health departments (82; 76.6%); medical practitioners or institutions (21; 19.6%) and nursing/immunisation professionals and other sources (4; 3.7%).

In undertaking this exercise, the Panel was mindful that the diagnosis of urticaria was equally if not more open to differing interpretation of symptoms and signs as anaphylaxis. A case in point is ADRS No. 244915, where the quite non-specific description of a rash reported by the parent of the patient as "itchy dots" was recorded using the reaction term, "urticaria" in the relevant section of the pro-forma submitted to the TGA by the state health department. The term "urticaria" was then picked up and used for coding in the ADRS database. It is not clear whether this was due to additional information obtained but not reported by the State reporter or simply differing classification terms being used. Thus, it was considered important to ascertain which reports of urticaria had been based on direct observation by trained medical staff. For the purposes of the analysis of jurisdictional distribution, "medically confirmed" cases of urticaria were those in which the primary reporter was a medical practitioner or institution. Such reports were assumed to be based on observation unless otherwise stated, although it is accepted that many of these reports may have been based on reported rather than observed skin changes.

However, because of the way in which information had been presented by NSW Health, it was often unclear how the diagnosis had been made (direct observation vs history alone) and by whom. The NSW Health reports were presented in the form of "clinical summaries", with no consistent way of identifying the primary reporter. Of the 82 reports submitted via health departments, the primary reporter could not be identified in 30 (36.6%) cases and in 13 of these 30 cases (43.3%) there was no evidence of medical attention having been sought. Furthermore, 24 (29.3%) reports submitted via health departments were based on information provided by the patient, a parent or relative and in a significant proportion of these (all but 6 cases) there was no evidence of medical attention having been sought. Thus, results are also presented according to whether there was evidence that medical attention had been received (but diagnosis not necessarily confirmed in cases where the primary reporter was not medically trained), recognising that this would likely overstate the number of true cases.

It can be appreciated from the Table that the ability to draw conclusions about the rate and distribution of urticaria cases across the jurisdictions is significantly impacted by the method of reporting used by NSW. Whereas the number of reports and therefore rates for the other states are similar irrespective of the criteria applied, the NSW results vary significantly.

Globally, 560 cases of urticaria were reported to MSD to the end of February 2008 as part of the post-marketing experience, with 27,326,195 doses having been distributed. This represents an "unadjudicated" rate of 20.49 cases per million doses distributed, compared with the "unadjudicated rate of 23.7 cases per million doses distributed in Australia. Interestingly, the rate of urticaria observed in the pre-market clinical trial program was much higher, with 51 cases in 14,304 patients (0.4%). This may be an indication of the role of observation and solicited reporting in a variable clinical syndrome such as urticaria.
The issue of hypersensitivity amongst Australian recipients of Gardasil has also recently been the subject of two papers published in the medical literature, outlining experience from three jurisdictional schools-based HPV vaccination programs. Kang et al 2008[19] evaluated cases

[19] Kang LW, Crawford N, Tang ML, Buttery J, Royle J, Gold M, et al. Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: retrospective cohort study. *BMJ* 2008;**337**:a2642.

of suspected hypersensitivity to Gardasil reported in Victoria and South Australia by skin testing and rechallenge. Schoolgirls with suspected hypersensitivity reactions, such as anaphylaxis, were referred to allergy centres for further evaluation using skin prick and intradermal tests for 4vHPV (Gardasil), bivalent HPV (2vHPV) or polysorbate 80, and subsequent rechallenge to confirm whether they were truly hypersensitive to Gardasil. A total of 25 of 35 girls with suspected hypersensitivity (after more than 380,000 doses administered in those states) agreed to further testing. Only 3 were found to have probable hypersensitivity to Gardasil, suggesting that most occurrences, especially those occurring more than 1-2 hours post vaccination, will not prove to be vaccine related. Eighteen were safely re-immunised with Gardasil, of whom one developed mild urticaria. Of the two anaphylaxis cases identified, one had a positive skin test. This patient had generalised urticaria following the first dose and anaphylaxis after the second dose of Gardasil.

In an earlier publication, Brotherton et al 2008[20] reported 42 notifications of suspected hypersensitivity following 4vHPV vaccination of NSW schoolgirls aged 15–18 years. The authors of the publication sought interviews with the first 26 of the 42 cases of apparent hypersensitivity and, of the 22 interviewed, 18 were judged by the expert panel to be certainly (3), probably (8), or possibly (7) due to vaccination. Of these 18, there were 13 with an urticarial rash, three with angioedema, two with blistering mucosal/skin rashes and one who had a localised immediate allergic reaction. As in Kang et al 2008, most reactions occurred after dose 1 (n=13), and 11 had a history of acute allergic reactions and/or atopic disease. Skin testing was not performed in this group of recipients but in the five who had received another dose, the reaction did not recur in one, recurred with the same severity in two and worsened in two.

Overall, this combined Australian experience, reported from the NSW and Vic/SA jurisdictional school-based HPV vaccination programs, demonstrates that hypersensitivity and, in particular, anaphylaxis is rare. However, immunisation providers need to be aware of the possibility of hypersensitivity and/or anaphylactic reactions and manage these appropriately.

The Panel noted and agreed with the ADRAC's previous assessment that:

- the absolute rate of anaphylaxis reported with Gardasil is relatively low; and
- the safety measures already in place to manage risks of anaphylaxis with Gardasil, including the requirements for parental consent and post-vaccination monitoring and the availability of rescue medications and dedicated follow-up clinics are appropriate.

4.4 Neurological adverse reaction reports

4.4.1 Identification of ADRS case reports of possible demyelination and autoimmune neuro-inflammatory disorders

An ADRS case line listing for neurological ADR reports received for Gardasil was compiled. The case line listing was then searched for reports describing possible demyelinating events and autoimmune neuro-inflammatory events using the following groupings of reaction terms:

[20] Brotherton JM, Gold MS, Kemp AS, McIntyre PB, Burgess MA, Campbell-Lloyd S. Anaphylaxis following quadrivalent human papillomavirus vaccination. *CMAJ* 2008;**179**:525-33.

1. multiple sclerosis, transverse myelitis, central nervous system inflammation or lesion, optic neuritis;
2. acute disseminated encephalomyelitis, encephalomyelitis, leukoencephalomyelitis, encephalitis;
3. neuropathy, peripheral neuropathy or Guillain Barré Syndrome;
4. ataxia, paresis, hemiparesis, monoparesis, palsy or paralysis; and
5. myasthenia gravis.

The results presented in this report are based on line listings held by the TGA as at 31 October 2008. A total of 9 reports were identified by search 1 (Table Thirteen, page 60), 3 by search 2 (Table Fourteen, page 61) and 4 by search 3 (Table Fifteen, page 62). In all of these reports Gardasil was the sole suspected drug. Search 4 identified 18 reports of potential significance. Four of these cases were also identified through searches 1 to 3 (i.e. the reports contained multiple, relevant reaction terms). Search 5 did not identify any reports.
All reports identified under searches 1, 2 and 3 were referred to the Panel neurologists for review and comment. Only selected cases from search 4 were referred to the Panel neurologists as these particular terms were non specific. For example, paresis and paralysis were terms used to record loss of function which may have been secondary to localised oedema and pain in the arm. Similarly, a report of a patient feeling as though she was paralysed was also recorded as paralysis, without any objective indication of motor weakness. Thus, cases identified through this search were first triaged within the TGA's Office of Medicines Safety Monitoring (OMSM) and only significant events in which there were corroborating physical signs or no alternative clinical explanation for the paresis were referred to the Panel neurologists for further review (3 reports in total). These particular cases are presented in Table Sixteen (page 63). A reconciliation of all cases identified through search 4 appears in Table Seventeen (pages 64-65). In all but two of the reports[21] identified by search 4 Gardasil was the sole suspected drug.

Where necessary, further diagnostic and case verifying information were sought from the treating neurologist by [redacted]. In addition, a copy of the neurological case line listing was provided to the Panel neurologists who were asked to identify any other ADRS reports they wished to review.

4.4.2 Review of case reports by the Panel neurologists

MS Case definition

The key diagnostic criteria adopted for MS were:

1. Clinically definite multiple sclerosis (CDMS) - clinical evidence of 2 separate lesions in different parts of the CNS which have occurred at different times, so called dissemination in time and space (Poser criteria);
2. Clinically isolated syndrome (CIS) or first demyelinating event (FDE) - patient has had only one clinical episode, in which dissemination in space may be shown by MRI or evoked potential studies and dissemination in time by repeat MRI. In cases where there is historical evidence of 2 or more attacks but objective clinical evidence of only one lesion, dissemination in space may be shown by MRI (McDonald criteria);

[21] In ADRS Nos 239356 and 245768 which were reports of facial palsy, the patient also received DTPa and varicella vaccination, respectively.

3. Acute Disseminated Encephalomyelitis (ADEM) – acute or subacute onset of an inflammatory and demyelinating process affecting multiple parts of the CNS following an exanthematous or infectious illness. However, it was noted that when ADEM occurs without preceding infection it may be impossible to disseminate from MS, in which case the diagnosis of MS depends on the demonstration of new lesions on MRI 3 to 6 months later.

At its meeting of 25 August 2008, the Panel agreed the criteria for case definition of *Gardasil-associated MS* were either CIS consistent with inflammatory demyelination with MRI confirmation, or CDMS or relapse of existing CDMS with MRI confirmation **within 6 weeks of vaccination**.

In choosing the six week window period post vaccination for its case definition, the Panel noted that in the paper by Sutton et al 2008 (see footnote 9), the period between vaccination and onset of events was within four weeks in all cases. Siegrist et al 2007[22], used time windows of up to 6 weeks, based on "biological plausibility" of causal association between exposure to a putative factor and onset/exacerbation of disease. Confavreux et al 2001[23] chose a two-month risk period in which vaccination might be considered to trigger a relapse in MS (RR 1.26) but, based on additional analyses at one month (RR 1.18) and three months (RR 0.58), concluded a one month post vaccination period was probably the most relevant period in patients with MS who had received inactivated vaccines.

Outcomes of the case reviews

Reports of Multiple Sclerosis and optic neuritis (Table Thirteen, page 60)

The ADRS database contained nine reports with reaction terms of "multiple sclerosis" and/or "optic neuritis", including the five cases reported in the paper by Sutton et al (see footnote 8).

The five cases reported in the MS Journal were stated by the authors of that paper to be noteworthy because they involved unusual presentations of MS. On review by the Panel's neurologists, all five cases were considered to meet the case definition. Two cases (ADRS Nos 242793 and 242796) were diagnosed with a first demyelinating event (CIS), one of whom (ADRS No. 242796) subsequently developed CDMS. The remaining three patients (ADRS Nos 236306, 242785 and 242789) had previously experienced clinically isolated episodes of neurological dysfunction and were diagnosed with CDMS at presentation. In three of the five cases patients presented with monosymptomatic presentation – one patient presented with pseudoathetosis of R arm with multifocal spinal cord disease with longitudinally extensive spinal cord lesion in addition to multifocal deep white matter lesions in the cerebral hemispheres (ADRS No. 242793); the second patient presented with global headache prior to developing transverse myelitis (ADRS No. 242785); and the third patient presented with acute hemiparesis (ADRS No. 242796).

Two of the five cases developed multifocal disease following immunisation – one presented with incomplete transverse myelitis within 24 hours and subsequently L optic neuritis 7 days

[22] Siegrist C, Lewis E, Eskola J et al. Human Papilloma Virus Immunization in Adolescent and Young Adults. A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions. *Pediatr Infect Dis J* 2007; **26**: 979-984.

[23] Confavreux C, Saddier P, Bourdes V and Vukusic S. Vaccinations and the Risk of Relapse in Multiple Sclerosis. *NEJM* 2001; **344**: 319-326.

later (ADRS No. 236306); and the second presented with incomplete transverse myelitis 4 days post immunisation followed by a brain stem syndrome 24 days later (ADRS No. 242789).

The neurologists concluded that the clinical presentations and subsequent course of disease in these five cases did not appear particularly unusual and that the likelihood of being able to discern a role of vaccination on the basis of specific clinical presentations was very low.

A further two reports (ADRS Nos. 243264 and 244364) were considered to have met the case definition for MS. In ADRS No. 243264 a 17 year old girl presented with a two day history of lower leg weakness and numbness and inability to walk unaided one week after Gardasil vaccination. Clinical examination demonstrated a mid thoracic sensory level and MRI showed transverse myelitis with approximately 8 cord lesions, with highest at C2 to C4. The lesions thought to most likely be inflammatory or demyelinating. She received 3 days of IV methyl prednisolone and made full recovery by day 6. CSF and serum samples taken during admission showed identical oligoclonal bands, resembling systemic infection. Sixteen days later she re-presented with a 3 day history of painful R eye, blurred vision and reduced VA, consistent with R optic neuritis. Once again she settled with IV methyl prednisolone and has remained well since. This report was considered to meet the Panel's case definition. However, this patient had also had an upper respiratory tract infection (URTI) preceding the onset of her initial symptoms, but the timing of the URTI in relation to the onset of the symptoms and the vaccination with Gardasil was unclear, with varying durations documented throughout the case records. Furthermore, the presence of matching oligoclonal bands in the serum and CSF is more suggestive of infection and therefore the possibility of a post-infectious demyelination syndrome cannot be ruled out.

In ADRS No. 244364 a 26 year old woman presented with optic neuritis and migrainous headache within 3 weeks of her first dose of Gardasil. On MRI examination there were lesions within the periventricular deep white matter bilaterally. This was considered to represent a first demyelinating event or CIS and the finding of white matter lesions increased the risk that this patient would progress to MS at some time in the future.

A final report of MS (ADRS No. 237812) was not considered to meet the case definition as it did not have a defined temporal relationship with Gardasil, occurring 9 weeks after vaccination.

Those reports considered to have met the Panel's case definition are highlighted by shading in Table Thirteen.

Reports of ADEM, leukoencephalomyelitis and encephalitis (Table Fourteen, page 61)

A total of 3 reports were retrieved by the search. One report (ADRS No. 243040), suggestive of viral encephalitis in a 26 year old woman, contained limited diagnostic information and the patient had declined key investigational procedures, such that the diagnosis is uncertain. A second report (ADRS No. 235453) was of ADEM characterised by agitation, confusion and ataxia and confirmed by MRI changes, but was of low biological plausibility as the event occurred some 82 days post vaccination dose. In the final report (ADRS No. 243038), a 21 year old patient with previously diagnosed relapsing, remitting MS developed ADEM 28 days after the second vaccination dose. This case was noted by the Panel neurologists as being of particular concern because it is most unusual for patients to develop ADEM in the

course of relapsing remitting MS. This case has been highlighted by shading in Table Fourteen.

Reports of neuropathy, including Guillain Barré Syndrome (Table Fifteen, page 62)

Four reports were identified by this search. Three reports contained the reaction term Guillain Barré Syndrome (GBS) (ADRS Nos 233239, 235044 and 243347). Of these, one was a case of self diagnosis in a 25 year old woman who had been admitted to hospital with pleurisy, weakness and incoordination (ADRS No. 243347). Neurological review has failed to confirm a diagnosis of GBS and the report has been recoded subsequently to remove reference to GBS. In a second case (ADRS No. 233239), the diagnosis of GBS had been changed since the time of reporting to chronic inflammatory demyelinating polyneuropathy (CIDP) on the basis of worsening condition and follow up nerve conduction studies. This patient was found to have experienced a febrile illness 6 weeks prior to the onset of neurological symptoms and have positive Mycoplasma serology with a rise in titre. Mycoplasma infection is known to be associated with GBS and is the more likely precipitant in this case. In the third case (ADRS No. 235044) the diagnosis of GBS was considered to be secure on the basis of patient's clinical course and confirmatory nerve conduction studies. This patient developed symptoms within 14 days of receiving her second dose of Gardasil and in the absence of a prior viral illness a causal relationship could not be excluded. This case has been highlighted by shading in Table Fifteen.

In the remaining report of peripheral neuropathy (ADRS No. 234391), a 16 year old woman was reported to have developed bilateral ascending sensory loss in both lower limbs but with normal muscle power and reflexes and no evidence of organic disease on investigation that included nerve conduction studies.

A fifth case (ADRS No. 246157), possibly of GBS was also identified, although not through this search. The report had been coded with the terms muscle weakness, hyperreflexia and paraesthesia. A 15 year old girl developed weakness in her feet one day after her third dose of Gardasil. She subsequently developed bilateral ascending weakness in both lower limbs to knee level and tingling in her upper extremities. She was admitted to hospital with a diagnosis of myopathy (?Guillain Barré Syndrome) of post infectious aetiology. Two weeks prior to admission she had suffered from a chest infection that required treatment with antibiotics. On examination she was found to have decreased lower limb power (right >left) on examination with hyperreflexia and intact sensation. No respiratory or gastrointestinal pathogens were isolated from throat swabs or faecal specimens and CSF examination was unremarkable. Importantly, nerve conduction studies were not performed and serological testing for Mycoplasma was not done. The patient was discharged from hospital after a period of rehabilitation during which her level of functioning was noted to be inconsistent with either an upper motor neurone lesion or a polyneuropathy. No definitive diagnosis was made. This was not considered to be a case of Guillain Barré Syndrome as reflexes were increased (whereas they should have been absent or at least decreased) and doubts were raised during her hospital admission about the organic nature of the symptoms.

Reports of ataxia, paresis, hemiparesis, monoparesis, palsy or paralysis (Tables 16 &17)

This search identified four cases that were also identified by other searches – ADRS Nos 235453, 242789, 242796 and 243264.

A further three cases were also selected for review by the Panel neurologists. In the first case (ADRS No. 230073), there was MRI evidence of neuritis of the C5, 6 and 7 nerve roots (brachyneuritis) as a cause of arm pain and numbness. However, there were additional, inconsistent leg symptoms that could not be explained, suggesting there was also a degree of somatisation in this case. The second case was a report of progressive left-sided sensory and motor symptoms in a 17 year old girl (ADRS No. 237037). However, the MRI was normal and no objective evidence of neurological pathology could be identified.

In the third case (ADRS No. 242877), a 13 year old US citizen, vaccinated in the USA and holidaying in Australia developed headache and exhibited abnormal behaviour and cerebellar signs (ataxia, dysarthria) 14 days following vaccination with the first dose of Gardasil. MRI findings were consistent with a diagnosis of cerebellitis. While in Australia the patient was treated for suspected Lyme disease, Listeria and possible ADEM. Serology was negative for Lyme disease and positive (but with no rise in titres) for Mycoplasma, Rickettsia and Q Fever (thought to be false positives). Clinically this patient had ADEM with evidence of inflammation within the cerebellum occurring 14 days after vaccination and therefore met the case definition for MS established by the Panel. This case has been highlighted by shading in Table Sixteen (page 63).

From Table Seventeen (pages 64-65) it can be appreciated there have also been seven reports of cranial or facial or Bell's palsy, with variable degrees of available information and therefore diagnostic certainty. Bell's palsy is not a demyelinating disorder. However, there are similar pathogenic mechanisms seen with brachyneuritis, which is known to be associated with vaccination. Bell's palsy has been reported occasionally with other vaccines but an association has not been definitively established[24].

4.4.3 Attempts to identify unreported cases of MS

In an attempt to identify all observed but as yet unreported Australian cases of MS, a letter was sent to members of the MS Interest Group of the Australian Association of Neurologists by [redacted]. No additional cases were reported in NSW, QLD, SA, WA, Tasmania, the Northern Territory or the ACT.

In Victoria, two cases were identified through this process. The first, a report of ADEM had already been reported to the TGA (ADRS No. 243038). The second case was a new case, in which a 23 year old woman presented in mid December 2007 with tingling in both her feet 15 days after receiving her first Gardasil injection. The tingling subsequently ascended to the base of her neck. MRI scanning performed a week after the onset of symptoms showed multiple sub cortical lesions consistent with demyelination. The patient was treated with Methylprednisolone and a follow up MRI in April 2008 showed no new lesions. At that time the patient remained clinically stable. This case was considered by the Panel to be a first demyelinating event (CIS), which met the Panel's case definition.

4.4.4 Overall summary of Australian cases of demyelination associated with Gardasil

A total of ten cases of CNS demyelination occurring in females aged 16 years to 26 years shortly after Gardasil vaccination have been identified in Australia to date. Nine of these cases were identified through the TGA's spontaneous adverse reaction reporting system.

[24] ADRAC 303 (September 2007) Minutes, Item 10.2.2.

Since late August, the Panel has liaised with Australian neurologists specialising in the treatment of demyelinating diseases in a preliminary attempt to ascertain whether there have been unreported Gardasil-associated cases. To date one additional case has been identified, but this approach has significant limitations as first, receipt of Gardasil may not be a routinely sought exposure in the neurological history-taking and second these inquiries relied on neurologist recall, so undetected cases cannot be excluded.

Six of the ten cases have been reported from NSW and five of those six were cases of multiple sclerosis referred to two Sydney neurologists with a specific interest in the disease. Of the ten cases of CNS demyelination, six were reports of new onset disease and four were reports of exacerbation of existing disease (either relapse of CDMS or CIS developing into CDMS):

New onset disease		*Exacerbation of existing disease*	
ADRS No 242793	NSW	ADRS No 236306	NSW
ADRS No 242796	NSW	ADRS No 242785	NSW
ADRS No 243264	Vic	ADRS No 242789	NSW
ADRS No 244364	NSW	ADRS No 243038	Vic
ADRS No 242877	NT (US citizen)		
Non ADRS case[25]	Vic (see 4.4.3)		

There has also been a single case of peripheral demyelination reported (a case of Guillain Barré Syndrome; ADRS No. 235044) occurring within 6 weeks of Gardasil vaccination.

4.4.5 Review of global reports

In its Gardasil Risk Management Plan (RMP) dated July 2008 (data lock point 29 February 2008), MSD noted they had received 17 reports globally of MS or optic neuritis, as follows:

> *Seventeen reports containing the terms multiple sclerosis and optic neuritis were retrieved and reviewed in detail. Patients ranged in age from 15 to 27, with median age of 17. The majority of the cases were reported from the United States and western Europe. In two of the cases, symptoms suggestive of multiple sclerosis were present prior to the patient receiving the first dose of qHPV vaccine. Of the remaining cases, 14 included information pertaining to the time of onset. In these cases, symptoms were reported from day 1 to day 90 following administration of qHPV vaccine. The most frequent time to onset of symptoms was 2 months following vaccination (n=6). Of the 15 cases where multiple sclerosis/optic neuritis was diagnosed after the patient received qHPV vaccine, nine included diagnostic information (MRI and/or CSF results) which supported a diagnosis of multiple sclerosis or optic neuritis*. (MSD's RMP Page 51)

The TGA sought and received MSD's global case listings of multiple sclerosis and optic neuritis for Gardasil as at 4 September 2008. At that time there were 43 cases reported worldwide, including 5 reports from Australia (ADRS Nos 234408, 242796, 237812,236306 and 243264). All reports of Australian origin were known to the TGA, but it is clear that not all Australian ADRS reports have been included among the MSD case listings and

[25] This report has subsequently been entered in the ADRS database as case number 246547.

furthermore, where cases had been included in the listing, in some the information was incomplete compared with the corresponding ADRS report.

Table Eighteen (pages 66-72) summarises the information as presented in the global reports. Analysis of these reports was difficult for a variety of reasons. Many reports were either incomplete (e.g. absence of patient age, dates of administration, date of onset of reaction etc) or diagnostically insecure (absence of corroborating investigative information) or confounded by the concomitant administration of other vaccines. The TGA has no ability to obtain further information other than through the sponsor company. Furthermore, in many cases the company did not expect to be able to obtain further information, particularly with respect to second and third hand reports. MSD's assessment of these reports was not expected until the next PSUR for Gardasil, which will not be finalised until January 2009.
Despite the limited information available and the difficulties in attributing causality, three of the global reports are suggestive of positive rechallenges (highlighted by shading in the table):

- WAES 0806USA08578 (row 1, page 68) – on the day of her first dose this 18 year old patient developed left sided anisocoria which resolved with no apparent treatment. On the day of her second dose, she again developed left sided anisocoria, this time associated with headache, syncope and dizziness. She was diagnosed by an optometrist as suffering from optic neuritis and had white matter lesions on MRI. However, two neurologists did not believe this was a case of MS;
- WAES 0803USA01333 (row 2, page 69) – 6 weeks after her second dose of Gardasil this 15 year old patient developed right optic neuritis which initially began to resolve over two weeks with IV prednisolone but required further treatment 4 weeks later because of ongoing visual problems. An MRI and SEP were reported as normal. The patient then had a recurrence of optic neuritis 5 weeks after her third dose of Gardasil, again requiring treatment with IV steroids. She has since had a further episode of optic neuritis some seven months after the third dose of Gardasil; and
- WAES 0801USA03199 (row 4, page 70) – this 17 year old patient experienced asthenia and paraesthesia of her right hand 7 days after her second dose of Gardasil. The patient recovered without any apparent treatment. The initial diagnosis was a "pressure lesion of the radial nerve" and no further investigation was performed. Twenty one days after her third dose the patient developed diplopia, headache, dizziness and fever, with a recurrence of the paraesthesia. Oligoclonal bands were found in the patient's CSF and MRI showed multiple demyelinated lesions in the periventricular medullary layer. A diagnosis of MS was made and treatment with high dose prednisolone gave good resolution of her symptoms.

4.5 New onset chronic disease of possible autoimmune aetiology

4.5.1 Identification of reports

An ADRS case line listing for ADR reports received for Gardasil was compiled. The case line listing was then searched for reports describing new onset of chronic disorders of potentially autoimmune aetiology. Search terms used and a summary of the cases retrieved are listed in Table Nineteen (pages 73-75).

A total of sixteen reports were identified by the search, of which two were subsequently found to be duplicates of other reports.

Of the fourteen original reports, two reports (ADRS Nos. 2375452 and 230283) described exacerbations of pre-existing disease. A third report (ADRS No. 228979) had been coded with the reaction term 'arthritis' but was considered, on review by the TGA, to in fact be an allergic-like reaction. This patient had experienced swelling of the R foot and wrist "as though she had been bitten". The swelling resolved within 24 hours with topical and systemic antihistamines, suggesting an allergic aetiology was more likely than an autoimmune inflammatory response.

The remaining eleven reports were considered to be cases of new onset diseases.

4.5.2 Reports of new onset disease

There were eleven reports of new onset chronic disease as follows and indicated by darker shading in Table Nineteen:

Connective tissue disorders 3	Rheumatoid arthritis 1 Polyarthritis 1 Antiphospholipid syndrome 1
Dermatologic disorders 5	Guttate Psoriasis 3 Alopecia 2
Endocrine disorders 2	Goitre 1 Lymphocytic hypophysitis 1
Gastrointestinal 1	Coeliac disease 1

Connective tissue disease

Three cases have been reported following vaccination with Gardasil. In the first case, a self report (ADRS No. 235066), a 23 year old woman was diagnosed with rheumatoid arthritis by a rheumatologist following the second dose of Gardasil. The latency period was not reported and no clinical detail or familial history was provided with the report. In the second case (ADRS No. 234501), a 13 year old girl developed bilateral upper limb polyarthritis of her wrists, MCP and PIP joints 10 days after receiving Gardasil (dose no. not provided). She was found to be antinuclear antibody positive and all other investigations were reported to be normal. In the third case (ADRS No. 236663), a 20 year old woman with history of juvenile rheumatoid arthritis developed a DVT 26 days after her second dose of Gardasil. Concomitant medication included the OCP. On investigation she was found to have anticardiolipin antibodies and elevated anti-beta 2 glycoprotein, consistent with antiphospholipid syndrome. The development of antiphospholipid antibodies by patients with autoimmune disease is known to occur and thus, the role of Gardasil is unclear.

Dermatologic disorders

Three cases of guttate psoriasis have been reported in association with Gardasil vaccination. ADRS No. 240128 was a report involving a 17 year old girl who developed mild guttate psoriasis following the first dose of Gardasil, which settled with promethazine and pinetarsol treatment. Following the second dose she developed more florid, widespread and intensely itchy guttae psoriasis. An ADRAC causality rating of "certain' was assigned on the basis of

the positive rechallenge[26]. In the second case, ADRS No. 235326, a 17 year old girl with no clinical or familial history of psoriasis developed guttate psoriasis (diagnosed by a dermatologist) of her trunk and legs 2 days after her first dose of Gardasil. Concomitant medication included Depo-Provera. A third case of guttate psoriasis was reported in a 17 year old girl with a history of Klippel-Trenaunay Syndrome (ADRS No. 229154). For 3 to 4 days following her first injection the patient was generally unwell with temperatures, sore throat and a stiff neck, which subsequently settled. 16 days post injection she developed a pruritic, raised and scaly rash over her arms that progressively involved her trunk and lower limbs. A dermatologist diagnosed guttate psoriasis which he thought was triggered by the vaccine.

There have also been two reports of alopecia. Neither report was well documented. In the first (ADRS No. 237051) a 26 year old woman developed a small patch of alopecia 18 days after her second dose of Gardasil. No further details are available. The second case (ADRS No. 244417) occurred 9 weeks after administration of a second dose of Gardasil to a 15 year old girl and was treated with i.m. cortisone by her GP.

Endocrine disorders

A solitary case of thyroid swelling has been reported (ADRS No. 235085). This occurred in a 14 year old girl who, one week after receiving her second dose of Gardasil, developed a recurrence of pain at the injection site, sore throat and viral-like illness. She subsequently noticed swelling of her thyroid, which was painful to touch, associated with tiredness, weight loss and headaches. A paediatric endocrinologist confirmed the presence of a small bilateral goitre and some mild cervical lymphadenopathy. The patient was otherwise clinically euthyroid and the endocrinologist initially thought she may have been suffering from post viral thyroiditis. However, inflammatory markers and antithyroid autoantibodies were negative. Thyroid function tests, ultrasound and thyroid uptake scan were all normal. On this basis subacute thyroiditis and Hashimoto's thyroiditis were considered unlikely. Convalescent viral serology was negative apart from evidence of previous Epstein Barr viral infection. At one stage her morning cortisol level and androgen profile was assessed because of the new onset of acne and some increased body hair, however these were normal. On last review by the endocrinologist, some 5 months after the injection, the cause of her symptoms had not been diagnosed and, because of persisting fatigue, the possibility of chronic fatigue syndrome (from which her sister suffers) was being considered.

The TGA has also received a report of lymphocytic hypophysitis occurring in a 19 year old woman following vaccination with Gardasil. This patient presented with headache and polyuria, consistent with diabetes insipidus, 14 days after her second Gardasil injection. Her symptoms progressively worsened and an MRI scan performed one month later demonstrated lymphocytic hypophysitis. ACTH, TSH, gonadotrophin and prolactin levels were all normal. The patient required hospital admission for high dose steroid therapy which, although

[26] Codes are assigned using the TGA document *Causality (Probability) Rating. ADRAC Database of suspected adverse reactions to drugs explanatory notes. Feb 1997. Last Modified 19 February 2004.* The codes are:
Certain – used if there is a positive rechallenge; or reaction occurs within 5 minutes of parenteral injection; or if there is an injection or application site reaction;
Probable – used if there is only one suspected medicine and the patient recovers without treatment following withdrawal of the medicine; and
Possible – used when there are multiple suspected medicines or if the patient has not recovered and has received pharmacological treatment.

successful in treating the headache, was poorly tolerated. In spite of continuing low dose steroid therapy, the patient's diabetes insipidus continued at last report some 10 weeks post onset. Lymphoid hypophysitis is a rare autoimmune disease of the pituitary gland, with a female preponderance, typically occurring in late pregnancy or post partum. There was no history of pregnancy or of any autoimmune disorders in this particular patient.

Gastrointestinal disorders

ADRS No. 240684 was a report of new onset Coeliac Disease three weeks after the first dose of Gardasil in a 12 year old girl who had previously been completely well with no family history of the disease. No further information has been able to be obtained for this particular case.

4.5.3 Exacerbations of existing disease

There were two reports that described exacerbations of pre-existing disease. These are indicated in Table Nineteen by lighter shading.

ADRS No. 2375452 was a report of a flare in rheumatoid arthritis in a 22 year old woman within a few days of vaccination, in which she experienced swelling of both wrists and MTP joints that required a tapering course of prednisone. She commenced treatment with methotrexate following review by her rheumatologist.

The second case, ADRS No. 230283, was a report of transient hyperglycaemia for a period of 24hrs following administration of the second dose of Gardasil in a 16 year old girl with Insulin Dependent Diabetes Mellitus. The transient loss of BSL control occurred in conjunction with tachycardia, palpitations and lip oedema that developed 30 minutes after the injection persisted into the evening that day. These additional symptoms are consistent with angioedema and could explain the transient loss of diabetic control.

4.5.4 Conclusion

The total number of cases reported is quite low compared to the number of doses distributed (and therefore estimated number vaccinated) and does not appear to be more than would be expected to occur spontaneously in this age group.

4.6 Reports of acute pancreatitis and hepatitis

4.6.1 Acute pancreatitis

Concerns over a possible link between Gardasil and pancreatitis were publicised widely in the media following the publication of a case report in the Medical Journal of Australia. In that case (ADRS No. 234616), a 26 year old woman developed a rash and fever 2 days after her first dose of Gardasil, for which she received treatment with promethazine hydrochloride and doxycycline. She subsequently developed severe, constant epigastric pain at day 4 post dose, associated with elevated serum amylase and lipase and CT evidence of pancreatitis without necrosis. All other investigations, particularly viral screening and MRCP were normal. The absence of any identifiable cause of the pancreatitis, the close temporal relationship with the vaccination and the development of a prodromal illness led the authors

of the report to postulate the pancreatitis was secondary to vaccination, although a coincidental illness causing pancreatitis could not be entirely ruled out and the causality was confounded by the prior administration of medication for treatment of the rash. However, the authors thought an autoimmune mechanism was possible, whereby molecular mimicry may have stimulated production of autoantibodies.

A search of the ADRS Gardasil case line listing revealed another six reports of pancreatitis, occurring in patients aged 13 to 25 years. One of these (ADRS No. 233681) was a report of epigastric pain and increased pancreatic enzymes, noted by the reporter to be consistent with mild pancreatitis, but not entered in the database with that reaction term. The nature and details of all the reports received by the TGA to 31 October 2008 are summarised in Figure One (page 76) and Table Twenty (pages 77-79).

Most reports were of single, acute episodes of pancreatitis with time to onset ranging from 1 to 141 days after Gardasil injection. There was no apparent clustering of the dose number or time to onset across the cases. There was a single report (ADRS No. 245551) of chronic pancreatitis occurring 1 day after the third dose of Gardasil in a 13 year old girl. The episode lasted for 8 weeks and required two hospitalisations. No other cause for the pancreatitis was found.

One self-reported case (ADRS No. 244981) detailed three, possibly four discrete episodes of pancreatitis, which were suggestive (but not definitive) of a possible positive rechallenge. This 25 year old woman experienced an episode of abdominal and chest pain 9 days after her second dose of Gardasil in October 2007. She consulted her GP, was treated symptomatically for gastroenteritis and recovered without any investigations having been undertaken. The patient experienced a further episode of abdominal and chest pain in February 2008, 125 days after the second dose. A diagnosis of pancreatitis was reported to have been made at that time. The patient subsequently received her third dose of Gardasil in mid April 2008. Three days later she again experienced severe abdominal and chest pain. Her serum amylase was found to be elevated at 792 U/L (RR 10-100). She consulted a gastroenterologist who diagnosed biliary colic with pancreatitis. A CT cholangiogram was performed after her condition settled and showed a normal biliary system with a suggestion of possible small calculi. In August 2008, 128 days after the third dose, she experienced a further episode of abdominal pain, accompanied by nausea and dry retching. On that occasion the symptoms were more severe and necessitated hospitalisation of the patient for treatment with analgesia and IV fluids for four days. Her serum lipase was elevated (2913 NR not reported) and abdominal ultrasound was normal. It was not clear whether serum amylase levels were measured. One week prior to this she had experienced a sore throat and flu-like symptoms for which she had taken antibiotics (name unknown). An MRCP, organised by another gastroenterologist in October 2008 showed no evidence of anatomical abnormality or calculi. The patient's current gastroenterologist considered the cause of the pain not to have been elucidated and wished to examine her at the time of any further recurrence.

Whilst acute pancreatitis is a relatively common disease (5.4 – 80 per 100,000), it is not a common presentation in young women or non-drinkers. Possible causative agents that would need to be excluded are gallstones and alcohol (which account for 70 – 85% cases), viral infections (cytomegalovirus, mumps, coxsackie, hepatitis, herpes simplex and varicella),

drugs (estimated to account for 0.1 - 2% cases[27]), tumours, hypercalcaemia, hyperlipidaemia, trauma and pancreatic duct abnormalities.

In five of the seven cases (ADRS Nos 233681, 234617, 244617, 244981 and 245713), the work up for potential causative agents was incomplete. The report for ADRS No. 245551 stated all investigations of the cause of the pancreatitis were normal, without providing any clinical detail. In the remaining report (ADRS 234616) the work up was complete, but the likely causality of the pancreatitis is confounded by the administration of promethazine hydrochloride (Phenergan) and doxycycline for treatment rash and fever, prior to its onset.

Four of the seven patients (ADRS Nos 233681, 234617, 244617 and 244981) had been taking the oral contraceptive pill[28]. There was no specific mention of oral contraceptive in the remaining three reports. In the published article associated with ADRS No. 234616 mention was made of intensive history taking (presumably including medication history) failing to identify any other cause. However, the prior administration of Phenergan and doxycycline seemed to have been overlooked. In the four cases with documented use of the OCP, none had that medication withdrawn and in three cases no further episodes have occurred, suggesting oestrogen-induced pancreatitis is highly unlikely. Furthermore, oestrogen-induced pancreatitis is thought to be linked with the hypertriglyceridaemic effect of oestrogen and the metabolic screens, including serum lipid profile were normal in ADRS Nos 234616, 234617 and, most importantly, in ADRS No. 244981, where recurrent episodes of pancreatitis had been described.

4.6.2 Acute hepatitis

The TGA has also received a single report of hepatitis in a 14 year old girl, with the onset of right upper quadrant and epigastric pain, nausea and vomiting occurring one day after her second dose of Gardasil. She presented to an emergency department on the day of the onset of her symptoms and her blood tests were found to be normal. The pain and nausea persisted and on re-presenting to hospital the next day she was found to have elevated transaminases consistent with hepatitis. The patient's past history included cholecystectomy for gallstones at age 8 years. Abdominal ultrasound was performed and showed no evidence of intrahepatic cholestasis. Serology for hepatitis A and B, EBV, CMV, adeno and enteroviruses were negative. The patient was hospitalised and the hepatitis resolved spontaneously over a two week period. She has remained well since.

4.6.3 Global reports of pancreatitis and hepatitis

MSD reported that they had received 10 reports of pancreatitis/acute pancreatitis from the following countries – USA 6, Australia 3 and Germany 1. These reports are summarised in Table Twenty One (pages 80-82). All of MSD's reports of Australian origin were known to the TGA and four of the TGA's ADRS reports (ADRS Nos 233681, 244981, 245551 and 245713) were additional to those included among the MSD case listing.

All but one of the reports of non-Australian cases lacked sufficient clinical information to enable the independent verification of the diagnosis of pancreatitis. In the report in which pancreatitis was clearly confirmed (WAES No. 0808USA04473; row 1 page 81), the

[27] Balani A and Grendell J. Drug-Induced Pancreatitis. Incidence, Management and Prevention. *Drug Safety* 2008; **31**(10): 823-837.

[28] Oestrogen-induced pancreatitis has been recognised since the 1970s. Balani and Grendell, ibid.

causality was considered to be due to hypertriglyceridaemia, probably associated with her obesity and concomitant use of oestrogen containing oral contraception. Perhaps the most notable case was WAES No. 0701USA00203 (row 1, page 80), in which it was reported the patient experienced pancreatitis (but no diagnostic workup information was provided) that recovered over 3 to 4 weeks after each of the three doses of Gardasil, suggestive of positive rechallenge.

The MSD global reports of hepatitis were similarly generally deficient in critical information, particularly with respect to the diagnostic workup (Table Twenty Two, pages 83-84). A total of 8 reports, excluding the Australian case (ADRS No. 244616) had been received by MSD. Among these, of note were (highlighted in the table by shading):

- a US report (albeit quite deficient in information) of autoimmune hepatitis (WAES No. 0701USA00228; row 2 page 83) occurring some time following the first dose and before the second dose of Gardasil;
- a detailed German report of hepatitis occurring 36 days after the second dose of Gardasil in a 14 year old girl who subsequently developed autoimmune haemolytic anaemia (WAES No. 0804USA02722; row 1 page 84); and
- another detailed German report of rhabdomyolysis and hepatitis occurring in an 18 year old girl approximately 9 weeks after her second dose of Gardasil (WAES No. 0803USA03411; row 2 page 84). This patient subsequently developed polyneuropathy (pain with slightly slowed velocities on NCS) in her lower legs, thought to be of a parainfectious aetiology, although previous serological testing for EBV, CMV, Borrelia, Coxsackie B virus and influenza and parainfluenza viruses had been negative

Overall, there were no global reports of pancreatitis or hepatitis with sufficient confirmatory clinical and diagnostic information to allow for a confident attribution of causality to vaccination with Gardasil.

4.7 Australian reports of vulvovaginal reactions

In February 2008, the ADRAC noted there had been twelve reports of vulvovaginal reactions. Since then it has been established that two (2) of the reports considered by the ADRAC were duplicates (ADRS Nos 234883 and 235391) and the TGA has received a further (2) two reports, bringing the total number of reports received to thirteen[29]. These reactions are summarised in Table Twenty Three (pages 85-87).

Two of the reports (ADRS Nos 230355 and 233734) describe candidiasis, which was identified in the 2008 application (see page 7) as the most common new condition arising in subjects following vaccination in the clinical trial program, with a rate of approximately 10%. A further two reports (ADRS Nos. 233544 and 244781) describe the onset of irregular menstrual bleeding on a background of previously regular cycles after the patient commenced immunisation with Gardasil. In the case of ADRS No. 244781, the irregular bleeding/spotting after doses one and two was associated with nausea, vomiting and headache. Following the third dose of Gardasil it was reported the patient had suffered an

[29] The terms included in the search for vulvovaginal reactions included vaginal ulceration, vulvovaginal ulceration, vaginal mucosal blistering, vaginal swelling, vulvovaginal discomfort, vulvovaginal disorder, genital ulceration, vulvovaginal candidiasis, vulvovaginal dryness, vulvovaginal human papilloma virus infection, vulvovaginal mycotic infection, vulvovaginal pruritus, vaginal haematoma, vaginal haemorrhage and anogenital warts.

"awful" period. This was coded on the ADRS database as being a positive rechallenge (and therefore of certain causality), but given the dosing regimen is also on a monthly cycle and menstrual irregularity is a relatively common feature in this age group, the association with Gardasil dosing could be entirely coincidental. Also, another two reports (ADRS Nos. 228983 and 235631) described the occurrence of vaginal irritation and itching in the presence of a more generalised rash and pruritus, suggesting the genital symptoms were part of an allergic type reaction.

There were also two reports (ADRS Nos 236132 and 238693) of the development of genital warts. In one of these (ADRS No. 236132) the report was of the development of new warts on the day of vaccination. The reference to "new" warts suggests the patient had previously suffered from genital warts and there was a coincidental flare up of an existing HPV infection. In the second such report, it was noted that the initial onset and subsequent proliferation of warts were temporally related to the dosing with Gardasil. Of note, Gardasil has no therapeutic efficacy for HPV types that may have previously infected a patient. Furthermore, the vaccine does not contain a live virus so there is no risk of cross-infectivity.

Of the remaining five cases, one report (ADRS No. 234004) of vaginal swelling, haematoma, blistering occurring on the day of vaccination, with subsequent ulceration was considered by the treating gynaecologist to have been secondary to trauma associated with recent use of an exercise bike. Three reports (ADRS Nos 234508, 234844 and 235391) all described genital ulceration occurring in girls aged 16 to 17 years, with no apparent cause found. In one of these cases (ADRS No. 234884) the patient was reportedly not sexually active and had an extensive work-up which excluded HSV, CMV, varicella zoster and STDs. Another patient (ADRS report 234508) was reported to have had one sexual partner, and she and her partner tested negative for HSV but the diagnostic workup was incomplete. Interestingly, there was also reference within the report to this patient having previously undergone testing for HSV, but the trigger for that testing was not reported, suggesting the problem could have pre-dated the first administration of Gardasil. In the third of this group of reports (ADRS No. 235391), the patient developed vaginal inflammation and blistering two days after her first dose of Gardasil which was concomitantly administered with hepatitis A, typhoid and influenza vaccines. No diagnostic information was provided.

In the remaining report (ADRS No. 235450), a 25 year old woman developed an erythematous and painful vulva 1 day after receiving an injection of Gardasil. No other clinical or diagnostic information was available, which precludes any meaningful assessment of causality.

Some of the reports of vulvovaginal lesions can be explained by other factors. In the remaining cases, the diagnostic work up appeared incomplete. None of the cases included screening for Epstein-Barr virus infection, which is prevalent in adolescents and can manifest with symptoms of vulval/vaginal ulceration. Furthermore, it is important to recognise that even after complete diagnostic work up, 25% of patients with genital ulcers do not have a laboratory confirmed diagnosis[30]. Also, during the ADRAC's discussion, the possibility was raised that vaginal blistering and consequent ulceration with HPV vaccine may be similar to a fixed drug reaction. This would be a particular consideration in the cases where no other explanation was found – i.e. ADRS Nos 234508, 234844 and 235391. However, there was

[30] Workowski KA and Bermann SM. MMWR Recomm Rep 2006; 55(RR-11):1-94.

no previous exposure in two of these cases (ADRS Nos 234844 and 235391) and it was not clear if there was blistering or previous exposure in ADRS No. 234508.

Overall, at this point, there is no clear evidence of an association between Gardasil and vulvovaginal reactions or ulceration.

4.8 Reports of convulsions/seizures

In May 2008 the ADRAC noted there had been thirty one reports of convulsions or seizures reported to the TGA. Following its in-depth review of the case line listing and actual reports, the ADRAC noted the majority of reports described seizures associated with syncope, rather than being associated with an underlying neurological disorder, and that further investigation was not warranted. By 31 October 2008, the data cut off for this report, the TGA had received a total of 38 reports from a total of 1202 reports (3.2%).

A review of the ADRS case reports revealed that three and possibly four reports were duplicates, each derived from different sources. Table Twenty Four (page 88) shows the key information available from each of the reports in question. It is almost certain that ADRS Nos 229411, 230318 and 230606 are duplicates given the commonality of the patient's first initial, location of the reporter, date of the reaction and the event itself. ADRS No. 229409, which is a third hand report, may also be referring to patient AW, having been made on the same day on the same radio program as the report documented in ADRS 229411. The report is of limited value and does not contain the minimum information normally required of an ADR report and, in the opinion of the Panel, should have been 'General Listed' anyway. On this basis, there have been only thirty five unique ADR reports in which the reaction term has been convulsion/seizure etc. A full review of these cases has been undertaken and the disposition of these cases is shown in Figure Two (page 89). Details of each report are summarised in Table Twenty Five (pages 90-94).

The time to onset of the seizure was reported in twenty two (22) cases - eleven were within 5 minutes of the injection (including four of immediate onset), a further five on the same day and six from day 2 onwards. The duration of the seizure was reported in only eleven cases - six lasted 20 secs or less, another two for up to a minute, two for 5 minutes and there was one case of prolonged seizure activity lasting for 40 mins (see discussion of ADRS No. 239274, below).

It can be appreciated from Figure Two and its accompanying table, that most of the events coded as 'seizure' or 'convulsion' fall into three main groups: those occurring in patients with past history of convulsion/seizure/epilepsy (n=9); those with a syncopal or functional component (n=17); and those with new onset epilepsy/convulsions without syncope (n=9).

There were nine patients who were reported to have a known history of convulsions or epilepsy. Time to onset of the convulsion was reported in six of the nine cases. In ADRS No. 240960 there was immediate loss of consciousness after injection, followed by a seizure lasting 20 seconds. Two other reports (ADRS Nos 230561 and 238844) documented the onset of convulsion within minutes of the injection, suggesting there may have been syncopal or functional element to the seizures in those cases, rather than a true exacerbation of seizure activity. In the remaining cases where the time to onset of seizure activity was documented, the latency periods were 1, 2 and 6 days. ADRS 230606 was a report of epilepsy complicated

by vertebral fracture in an 18 year old girl with a three year history of absence seizures. Two days after her injection after a night out with friends she was found calling out in pain and incontinent by her mother. She was hospitalised and found to have sustained T5/T6 fractures. EEG monitoring showed several absence seizures. Subsequently 8 days later the patient experienced a generalised tonic clonic seizure lasting for 5 minutes. The final diagnosis was juvenile absence epilepsy. ADRS No. 240044 was a report of an episode of headache, fever, vomiting and visual disturbance occurring in a 12 year old girl 6 days after her second dose of Gardasil. The patient had past history of febrile convulsions. The reaction term 'syncope' was also used to code this report but there was a questionable history of convulsion post vaccination and of loss of consciousness associated with the headache. The treating diagnosed migraine headache on the basis of headache, associated visual disturbance and vomiting and the family history of migraine. The timing and nature of the events and the questionable history of convulsion and loss of consciousness suggests syncope was not a feature of this event.

With respect to those reports of convulsion considered to be of syncopal or functional origin, there were nine reports that had been originally coded using the term 'syncope' in the ADRS database and a further eight reports that were entered in the database without any reference to syncope but following independent review in the OMSM were adjudicated as having either a syncopal or functional element. With respect to those cases already coded with the term 'syncope', the timing onset of the event, the symptoms and signs reported and the duration of the events were consistent with syncope (i.e onset either immediately or within a matter of minutes and the events were self limiting within secs to minutes). In addition to ADRS No. 240044 (discussed above), another of the reports coded using the term syncope requires further comment. ADRS No. 235992 described two episodes of syncope in a 27 year old woman that occurred 12 hours and 3 weeks after her third dose of Gardasil. She was subsequently found to have low blood pressure and the syncope and convulsion is more likely to be causally related to that than the immunisation procedure itself.

The eight reports that were also adjudicated as being of syncopal or functional origin were done so on the basis of the immediacy of onset, short duration of symptoms, the symptomatology and signs exhibited (e.g. report of feeling faint, feeling dizzy, feeling cold and clammy or patient being observed to have fainted, slid off chair) and the sequence of events – faint or loss of consciousness followed by fitting. During their review of reports of convulsion in early 2008, the ADRAC members particularly noted ADRS No. 239274, which described a 12 year old girl who 5 minutes 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." The ADRAC members noted that the patient remained neurologically normal throughout the course of the event and considered the characteristics and timeframe of the events were inconsistent with true epileptic-type convulsions and agreed that a diagnosis of "functional seizures with anxiety" was more appropriate.

Only nine reports had neither a past history of convulsions nor any apparent syncopal or functional element. One of these (ADRS No. 235442) was a report of convulsions, diarrhoea, vomiting and malaise in a 20 year old patient who had abruptly ceased treatment with escitalopram oxalate, an SSRI, 6 days earlier. The actual period between administration of Gardasil and the onset of convulsions was not recorded. The symptoms and signs reported are

consistent with SSRI withdrawal and this would be a more plausible explanation in this case. In the remaining seven reports the quality of information was variable and in many cases there was no actual description of the seizure or of any investigations performed and these cannot be assessed any further. Time to onset of convulsions was reported in six of the seven cases and ranged from "hours" to 4 weeks. Two patients were stated to be undergoing further neurological assessment at the time of reporting.

4.8.1 Global experience of convulsions with Gardasil

In its Risk Management Plan dated July 2008, MSD reported there had been 180 reports of convulsion or Grand Mal convulsion reported as part of its worldwide adverse experience system (WAES) but 28 reports included too few details to conduct a proper assessment[31]. Of the remaining 152 reports, 84 (55%) described episodes of syncope and 23 (15%) included concurrent medical conditions/medical history of seizure or epilepsy. Time to onset was reported in 154 reports, with 96 (62%) events occurring within 10 minutes of vaccination, 28 (18%) occurring on the same day as vaccination and the remainder scattered between 2 and 88 days after the dose without any temporal clustering. The duration of the event was reported in 75 of the 180 reports. All but one case lasted 5 minutes or less with 33 (44%) lasting less than 30 seconds.

5. Epidemiological analysis of CNS demyelination

A total of ten cases of CNS demyelination occurring in females aged 16 years to 26 years in a six week period after Gardasil vaccination have been reported in Australia to date. There has been a preponderance of cases in NSW with a total of six cases, five of which were reports of multiple sclerosis from one clinic in Sydney. There have been no other published reports of multiple sclerosis from countries that have implemented HPV vaccination programs, although a number of previous studies have evaluated the risk of multiple sclerosis following vaccination, especially hepatitis B vaccination and no significant association has been observed[32,33].

Cases of multiple sclerosis must be viewed in the context of secular trends over time, with a progressive increase in recognized multiple sclerosis in Australia and overseas. In addition there are well-documented higher rates in colder climates[34,35,36]. Given this particular fact, and the preponderance of observed cases in NSW, it was considered appropriate to limit the Panel's epidemiologic analysis to the expected incidence of MS-like events in the female

[31] MSD reported that a further 68 cases were received in the 3 months prior to the data cut off date of 29 Feb 2008 for its RMP update which were not included in its analysis. Forty (59%) of the additional 68 cases involved either syncopal elements or a medical history which included convulsion/epilepsy or in one case a history of head trauma with chronic infarct and angioma.

[32] Mikaeloff Y, Caricade G, Rossier M et al. Hepatitis B vaccination and the risk of childhood-onset multiple sclerosis. *Archives of Pediatrics & Adolescent Medicine* 2007; **161**: 1176-1182.

[33] Mikaeloff Y, Caricade G, Assi S et al. Hepatitis B vaccine and risk of relapse after a first childhood episode of CNS inflammatory demyelination. *Brain* 2007; **130**: 4-10.

[34] Barnett M, Williams D, Day S et al. Progressive increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: a 35-year study. *Journal of Neurological Sciences* 2003; **213**: 1-6.

[35] Ranzano F, Perini P, Tzintzeva E et al. Increasing frequency of multiple sclerosis in Padova, Italy; a 30 year epidemiological survey. *Multiple Sclerosis* 2003; **9**: 387-392.

[36] Grimaldi L, Palmeri B, Salemi G et al. High prevalence and fast rising incidence of multiple sclerosis in Caltanisetta, Sicily, Southern Italy. *Neuroepidemiology* 2008; **28**: 28-32.

population receiving Gardasil in NSW. However, given the likely under-reporting of adverse events and the fact that vaccination history may not be routinely sought, the Panel was concerned that the Australian case ascertainment could be less than complete. Thus, several indirect indicators of the incidence or prevalence of demyelinating disease were also examined to see if there were any upward trends following the introduction of the Gardasil immunisation program. The chosen markers were the ordering of MRI scans for detection of demyelinating disease and the *de novo* prescribing of specific drugs used in the treatment of these conditions. Furthermore, as the background incidence of autoimmune neurological disorders is relatively low, an additional examination of new onset Type 1 diabetes mellitus, a relatively common autoimmune disease, was performed to increase the chance of detecting any evidence of Gardasil triggering autoimmune disease.

5.1 Expected incidence of MS like events in population receiving HPV vaccine in NSW

5.1.1 Methodology

In the New South Wales general practice-based program 347,568 doses of HPV vaccines were distributed in 2007[37]. Based on recent data from the Ausimmune study[38] site in Newcastle, the annual incidence of first demyelinating events (FDEs) was 7.4 per 100,000 person years , based on 9 events in a female population of 12,162 between the ages of 18 and 27 years (personal communication, [redacted]). The expected incidence in New South Wales has been calculated from two scenarios, A and B, based on the observed incidence of FDE in Newcastle. A third scenario (Scenario C) was created using reported incidence of MS in a younger female population reported from the UK[39]. In all three scenarios it was assumed that the distribution of doses between months was equal with minimal variation from schedule for recipients of the HPV vaccine. Thus, the second dose was administered 2 months and the 3rd dose 6 months after the first dose.

Scenario A

It was assumed that the administration of doses started 3 months after the initial roll out in April, with first vaccinations starting in July and that all distributed doses were administered. This will result in 60% of the doses over the 6 months (July to December) being 1st doses and 40% second doses, second doses starting 2 months later in September and administered over 4 of the total of 6 months available (6x doses given as first and 4x doses given as second between July 2007 and December 2007 with x being the equal number per month). Applying these percentages to the total doses distributed, 208541 persons received at least a 1st dose and 139027 persons received a second dose and no one received a third dose in 2007.

	Jul	Aug	Sep	Oct	Nov	Dec
1st	✓	✓	✓	✓	✓	✓
2nd	-	-	✓	✓	✓	✓
3rd	-	-	-	-	-	-

[37] Brotherton J, Gold M, Kemp A et al. Anaphylaxis following quadrivalent human papillomavirus vaccination. *CMAJ* 2008; **179**: 525-533.

[38] The Ausimmune Study is a case-control study involving approximately 1000 people across Brisbane city, the Newcastle region, the Western Districts of Victoria and Tasmania, intended to examine how environmental factors influence immune diseases and how immune disorders vary by latitude across Australia.

[39] Alonso A, Jick S, Olek M et al. Incidence of multiple sclerosis in the United Kingdom: Findings from a population-based cohort. *Journal of Neurology* 2007; **254**: 1736-1741.

Scenario B

It was assumed that administration started immediately after the first roll out, in the month of May. With the same assumption of equal distribution across months for first, second and third doses an estimated 50% of doses were first doses, 37.5% second doses and 12.5% 3rd doses (8x first doses from May to December, 6x second doses from July to December and 2x third doses from November to December with x being equal number administered per month). This results in: 173,784 persons receiving at least a first dose: 130 338 persons a second dose: and 43,446 persons receiving the third dose.

	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1st	✓	✓	✓	✓	✓	✓	✓	✓
2nd	-	-	✓	✓	✓	✓	✓	✓
3rd	-	-	-	-	-	-	✓	✓

Scenario C

The MS incidence rate observed in a UK population-based study[14] was applied to females aged 15 to 18 years in the NSW school-based program. The expected number of MS like cases was estimated from the total doses (269 680) documented as being administered in this program (dose1, n=95 006; dose 2, n=91 289; dose 3, n=83 845) and the enrolled school population in 2007 (n=114 000)[13]. In the UK study, only incident cases of MS were included. A case was considered incident if the first diagnosis was MS (ICD code 340.0). The MS cases were classified into definite, probable, possible and not MS. The mean (median) time between first symptoms and last examination in the 438 confirmed cases was 5.6 (5.4) years. The estimated incidence rate of MS was the ratio of the number of newly diagnosed MS cases in a particular age- and sex- stratum divided by the number of person-years in that stratum. The study reported an overall incidence rate of MS in women adjusted to the world population as 7.2 (95% CI 6.5, 7.8) per 100,000. The estimated lifetime risk from birth of an MS diagnosis was 5.3 per 1000 in women.

In all scenarios, the Poisson distribution and 95% confidence intervals were used to estimate the expected number of MS diagnoses for different women receiving at least 1 dose and those receiving at least 2 doses under different observation periods. The observation periods were broken into 3 sets. The first at 6 weeks corresponds to after the first dose but before the second dose, the second at 26 weeks corresponds to after the second dose but before the 3rd dose and the third at 52 weeks corresponds to after the 3rd dose. The estimates also used three levels of coverage - 100%, 80% and 60%.

5.1.2 Findings

Scenario A

The results for Scenario A are shown in Tables Twenty Six and Twenty Seven (page 95). In Scenario A, the expected number of cases was 6.2 (95% CI 2.8-11.7) among females in the age group of 18 to 27 who received at least 1 dose in 2007, with doses starting in July and observation for a 26 week period. For females aged 18 to 27 who received two or more doses in 2007 and were observed for a 26 week period, the expected number of cases was 4.1 (95% CI 1.9-7.8). The confidence bounds around this estimate would accommodate substantial under-ascertainment of cases.

Scenario B

The results of Scenario B are shown in Tables Twenty Eight (page 95) and Twenty Nine (page 96). In Scenario B, it is estimated that for females in the age group of 18 to 27 who

received at least 1 dose in 2007 with doses starting in May and observed for a 26 week period, the expected number of cases is 5.1 (95% CI 2.4-9.8). For females aged 18 to 27 who received two or more doses in 2007 and were observed for a 26 week period the expected number of cases is 3.9 (95% CI 1.8-7.3).

Scenario C

The results of Scenario C are shown in Tables Thirty and Thirty One (page 96). In Scenario C, it is estimated that among females 15 to 18 years who received one or more doses in 2007 and were observed for a 26 week period, the expected number of cases is 0.4 (95% CI 0.1-1.2). Expected numbers of cases in all enrolled females observed for a 26 week period, was 0.5 (95% CI 0.1-1.5).

5.1.3 Conclusions

If the six reported cases from NSW represent complete ascertainment in that state, the four cases occurring in women aged 18-27 years (ADRS Nos 236306, 242785, 242796 and 244364) would be within the expected number of cases of demyelinating disease in females in that age group who received at least one dose (estimate of 4.1; 95% CI of 1.9 to 7.8) in the absence of any association between Gardasil and demyelination. For the school-age group, 15-18 years, 2 cases within a 6 month period (ADRS Nos 242789 and 242793) is above the 99% confidence limits for expected cases but this estimate is very imprecise and relates to a much smaller population with a much lower incidence of FDEs. The precision of estimates may be improved by expanding the area and time period of observation as well as maximising case ascertainment but will still be hampered to a significant extent. The Panel noted that a similar exercise relating to MS following a school-based hepatitis B vaccine program in British Columbia, Canada, did not demonstrate any significant association.

5.2 Analysis of indirect indicators of the prevalence and incidence of demyelinating disease

5.2.1 MBS data on the ordering of MRI scans for detection of demyelinating disease

The ordering of MRI scans for demyelinating disease ('dd') was examined using MBS data for NSW/ACT and VIC/TAS in financial years starting July 2004 and finishing June 2008. It was assumed that any MRI scan processing related to a post-Gardasil episode would be unlikely to occur in the first half of 2007, given the fact that dosages were only particularly widespread from April 2007 and it would be a recurrent dose rather than initial that would be more likely to be linked to demyelinating disease. Thus, it is likely there would be a delay in any apparent upward trending due to the dosing schedule, any latency effect and the fact that the MBS data are based on processed claims - again with a time delay.

The mean number (s.d.) of scans ordered for demyelination per 100/000 females under 35 were: 28.4 (39.90) in 2004/05; 33.9 (46.48) in 2005/06; 37.6 (52.48) in 2006/07 and 72.1 (218.12) in 2007/08.

The age and sex patterns for patients having 'dd' scans appeared as expected. There was a borderline increase (p=0.07) in 'dd' MRI scans ordered in 2007/2008 versus the three year period prior and this was most evident for females between 25-34 in Victoria. The mean difference in the number of scans ordered, using 2004/2005 as a baseline was: 5 more in

2005/6 (p=0.8); 9 more in 2006/7 more (p=0.7); and 44 more in 2007/8 (p=0.095). However, MS incidence rates are known to be increasing over time. Although unlikely, it could be that there was effect modification by age with the 25-34 age group being particularly vulnerable to demyelinating triggers and the 25 and 26 year olds within this group having catch up Gardasil doses. Thus, on the basis of the suggestion of an increase in 2007/8, a role for Gardasil can not be fully excluded with this quality of data.

5.2.3 Conclusions

These data, although limited, did not suggest any major change in the occurrence of demyelinating illness among females aged 12-27 years, the vaccine target population, since the introduction of the vaccination program. However, changes of a lower magnitude would still be important to identify and may not be detected by these available systems.

5.3 Analysis of new onset Insulin Dependent (Type 1) Diabetes Mellitus

5.3.1 Methodology

An analysis of new onset insulin dependent (type 1) diabetes mellitus was undertaken using 2003-2007 data from the National Diabetes Services Scheme (NDSS), compiled by the Australian Institute of Health and Welfare (AIHW). NDSS data were used in preference to data from the National Diabetes Register (NDR), which is considered to be the highest quality data, because NDR data for calendar year 2007 had not been compiled by the AIHW at the time of writing this report. A key objective of the analysis was to ascertain if there was any discernable upward trending in the number of newly diagnosed cases after the

introduction of widespread vaccination in April 2007. This was not possible with the available NDR data. As the largest data source for the NDR, the NDSS is likely to be a good proxy but with some limitation:

- at the national level, the NDSS numbers were higher than the NDR numbers in 2003 to 2005 by the following amounts – 119 in 2003, 20 in 2004 and 14 in 2005 – with the narrowing of the difference in 2004 and 2005 reflecting the introduction of the new NDR consent arrangements for NDSS registrants from late 2003. In 2006, the NDR had 9 more cases than the NDSS, which might be accounted for by cases provided by the Australian Paediatric Endocrine Group (APEG) that are not registered on the NDSS; and
- when the data are broken down by state of diagnosis, there are 918 NDSS cases with an unknown state of diagnosis compared with 411 NDR cases with an unknown state of diagnosis. This probably reflects the fact that for NDR data for 0-14 year olds, where the AIHW has information for a registrant provided by both APEG and the NDSS, it assigns state of diagnosis to be equal to the APEG state of diagnosis if it is known.

The NDSS data provides counts of 'derived' rather than 'reported' Type 1 diabetes. The reason for this is that reported diabetes type may not always be reliable, particularly with people reporting Type 1 diabetes when they actually have Type 2 diabetes. Therefore, to obtain a more accurate measure of type of diabetes, the AIHW applies an algorithm that assesses 'reported type of diabetes' based on age at diagnosis and the period of time between diagnosis and date of first insulin use to create a 'derived type of diabetes'.

5.3.2 Results

The number of female patients with new onset disease were calculated for each month from January 2003 to December 2007 in three age categories - <15yrs, 15 to 24 yrs and 25 to 30 years – for Australia (Figure Seven, page 99) and the two largest States, NSW (Figure Eight, page 100) and Victoria (Figure 9, page 100). The slope of regression lines and average monthly numbers for the periods January 2003 to March 2007 (pre-Gardasil rollout) and April 2007 to December 2007 (post Gardasil rollout) were also calculated. There were no statistically significant increases in the average number of new cases of Type I diabetes mellitus per month following the roll out of the Gardasil immunisation program in any of the age groups across Australia and Victoria. In NSW there was an increase only for the 15 to 24 year age group (3.7 to 5.8 cases per month), however, this was largely due to a single high score for June 2007. The number of new cases was not sustained beyond that point and the number of new cases in the subsequent months fell back to pre-immunisation program levels, suggesting no major change in the occurrence of new onset Type I diabetes mellitus following the roll out of the Gardasil immunisation program.

6. Overall assessment of currently available efficacy and safety data

At the time of the writing of this report, in excess of 13,000 subjects had received at least one dose of Gardasil in the sponsor's clinical trial program and almost 10 million individuals had been vaccinated globally (based on an assumption of a three dose course) since Gardasil's first marketing approval.

Data submitted across the three applications received by the TGA to date have consistently shown prophylactic use of Gardasil with a 3 dose regimen at 0, 2 and 6 months is highly effective in 18 to 26 year old women at reducing the risk of them developing:

- new and persistent HPV 6, 11, 16 and 18 infections;
- HPV 16 and/or 18 related CIN 2/3 and /or AIS or HPV 6, 11, 16, 18 related VIN2/3 and/or VaIN 2/3; and
- HPV types 6, 11, 16 or 18 CIN 1, genital warts, perianal warts, VIN 1, VaIN 1 (noting that these conditions are not predictive of cervical, vulval or vaginal cancer).

CIN 2 or 3 or AIS precede invasive cancer and can be used as surrogate markers for the development of invasive cancers. Furthermore, Gardasil vaccine administered as a three dose schedule is immunogenic and produces elevated titres of anti-HPV antibodies compared to those observed in subjects receiving placebo and those who have naturally acquired infection. However, if a woman is already infected with an HPV type included in Gardasil, giving the vaccine will not affect the natural history.

The safety data provided in the updated clinical trial reports and from extensive post marketing (non study) exposure show that Gardasil is generally well tolerated with most reported events being procedural complications, administration site reactions such as soreness, swelling, redness, and systemic events such as headache, nausea, rash and dizziness. Several issues have been identified through the sponsor's post marketing surveillance system and these include medical device malfunction of the pre-filled syringe[40], the potential for exposure during pregnancy and the occurrence of hypersensitivity reactions such as anaphylactic/ anaphylactoid reactions, bronchospasm and urticaria. In relation to hypersensitivity reactions, the Panel concluded that the combined Australian experience, reported from three jurisdictional school-based HPV vaccination programs, demonstrates that hypersensitivity and, in particular, anaphylaxis is rare. This is supported by data generated through the CDC's Vaccine Safety Datalink in the USA. However, immunisation providers still need to be aware of the possibility of hypersensitivity and, in this regard, appropriate safety measures are already in place to manage risks of anaphylaxis with Gardasil, including the requirements for parental consent, the use of post-vaccination monitoring, the availability of rescue medications and the existence of dedicated follow-up clinics. Important potential risks identified by the sponsor and regulatory agencies (including, in Australia, through the deliberations of the ADRAC) include Guillain Barré Syndrome, multiple sclerosis, convulsions, pancreatitis and the potential for Gardasil to trigger autoimmune conditions. Based on its analysis of spontaneous ADR reports in Australia and the outcomes of passive and active surveillance activities in the USA, the Panel believes that, at present, there is no firm evidence of a causal relationship between the administration of Gardasil and any of these conditions but the occurrence of such events must remain under careful scrutiny by the sponsor and regulatory authorities.

The Panel particularly noted the intensive active postmarketing surveillance activities that have been undertaken in the USA. It is reassured by the recently released findings from the CDC's Vaccine Safety Datalink that showed no evidence of elevated risk for Guillain Barré Syndrome, seizures, stroke, syncope and allergic reactions in patients who received the vaccine.

[40] This issue has been specifically identified in MSD's Risk Management Plan and is covered further in section 7.1 and Table Thirty Two A and involves premature activation of the safety shield used to prevent needle stick injuries. The problem appears to be largely due to unfamiliarity with the safety device component of the pre-filled syringe.

It is also clear that data limitations identified at the time of original marketing approval are generally being addressed by the sponsor through ongoing clinical studies and current and planned post marketing epidemiological studies. Issues identified from both ongoing clinical trials and post marketing surveillance have been factored into the sponsor's Risk Management Plan, which contains a detailed Action Plan for each safety concern (see Section 7.1, below).

The TGA registered Gardasil on the basis of a favourable benefit-risk balance. The evidence currently available from ongoing clinical trials and intensive global post marketing surveillance activities does not suggest that the safety profile of the product has altered significantly. The Panel has therefore concluded that no additional regulatory action is required at this stage.

Specifically with regard to demyelinating disorders, based on the currently available evidence, the incidence of demyelinating disorders amongst recipients of Gardasil vaccine in Australia is not demonstrably higher than would be expected by chance alone. This is especially so in the context of the large Gardasil population program targeting a group (young adult women), among whom the incidence of demyelinating disorders is well known to rise sharply between the ages of 16 and 27 years. However, in individual cases, it is not possible to determine from the data presently available whether receipt of Gardasil vaccine triggered the demyelinating event or whether the event occurred independently. It is important to note that the design and size of the pre-marketing clinical Gardasil trials did not allow prior evaluation of this issue. Furthermore, there is no active monitoring system in place in Australia that could precisely and accurately identify cases in a systematic way from the vaccine-targeted population as they arise. In view of the serious nature of demyelinating events and the uncertainty over complete case ascertainment, this issue requires more rigorous evaluation and it is recommended the TGA should ensure an appropriate active surveillance program for Gardasil is established in Australia (see Section 7.2, page 45).

7. Future surveillance and risk minimisation

7.1 Review of the current Risk Management Plan for Gardasil

As part of its Terms of Reference, the Panel was asked to provide advice on the adequacy of existing and pharmacovigilance activities (as reflected in the sponsor's Risk Management Plan (RMP)[41]). Accordingly, the Panel reviewed MSD's document titled *"Gardasil (Quadrivalent Human Papillomavirus [types 6, 11, 16, 18] Recombinant Adsorbed Vaccine) Updated Risk Management Plan Volume 1 of 1, July 2008*. The document was presented in an EU format and included the analysis of data held by MSD as at 29 February 2008 and details of Action Plans for dealing with:

[41] An RMP is meant to document a starting point or 'specification' of what is already known at the time of marketing approval and what is required to extend safety knowledge after the medicine is marketed. The EU Risk Management Plan (RMP) for medicines has two parts. The first part contains the *Safety Specification*, which summarises the safety profile of the medicine at that particular point in time and the *Pharmacovigilance Plan* (PP), which is based on the Safety Specification. In the second part, on the basis of the Safety Specification, a company is required to consider the need for additional risk minimisation activities. As more information becomes available following marketing of the product the safety specification is updated and the Pharmacovigilance Plan amended to reflect new proposed activities, such as Action Plans.

- Important identified risks (Table Thirty Two A, page 101):
    - exposure during pregnancy;
    - medical device malfunction;
    - hypersensitivity;

- Important potential risks (Table Thirty Two B, page 102):
    - viral type replacement;
    - Guillain Barré Syndrome;
    - conditions of special interest, including immune thrombocytopaenic purpura, autoimmune haemolytic anaemia, uveitis, type 1 diabetes mellitus, SLE, Guillain Barré Syndrome, rheumatoid arthritis, juvenile rheumatoid arthritis, Hashimoto's Disease, Grave's Disease, multiple sclerosis, ADEM, optic neuritis and other demyelinating disorders of the CNS; and

- Missing information (Table Thirty Two C, page 103):
    - long term effectiveness and immunogenicity;
    - long term safety; and
    - unanticipated safety signals.

Tables Thirty Two A, B and C summarise the details and objectives of each Action Plan and the Panel's assessment of the adequacy of these activities. On the whole, the Panel considers the actions proposed by MSD to be warranted and appropriate. A specific action plan has not been proposed for the potential risk of pancreatitis, but this would be covered by the broad action plan for detecting unanticipated safety signals, through routine pharmacovigilance activities such as monitoring of spontaneous adverse event reports and published literature, through the surveillance study being undertaken in the US Managed Care Organisations, and through the long term follow-up study involving the Nordic registries. It is not considered that any additional activities are required for this issue at present.

It was noted by the Panel there are two large post market surveillance studies currently underway. The first is an observational database study in women receiving Gardasil being conducted at two large Managed Care Organisations in the California. By February 28, 2008, 40,580 subjects aged between 9 and 26 years had received at least one dose and 155,000 subjects of any age had received at least one dose.

The second long term study is being conducted in Norway, Sweden, Denmark and Iceland to examine the impact of Gardasil vaccination on the incidence of cervical, vaginal and vulval cancers and their precursors as well as congenital abnormalities of babies born to mothers with exposure to Gardasil during pregnancy. To date a total of 102,999 doses of Gardasil have been administered to subjects included in the registry. Analysis of the data will involve the use of case definitions currently used in clinical practice in each of the 4 countries (no external adjudication) and will be compared to stratified national data in the 4 countries involved. Both studies will comprise general safety surveillance of events occurring within 60 days of each vaccine dose, surveillance for inadvertent vaccination during pregnancy, and surveillance for selected new onset autoimmune disorders, including multiple sclerosis.

It is also apparent that, at the request of the European Committee on Human Medicinal Products, MSD will use the French "PGRx System®" [42] for the surveillance of Guillain Barré Syndrome and conditions of special interest such as systemic lupus erythematosis, rheumatoid arthritis, acute disseminated encephalomyelitis and CNS demyelination/multiple sclerosis via a series of prospective case control studies. The status of the proposal at this stage is exploratory only and the protocol is not expected to be finalised until Q1 2009 (personal communication from Lynne Dudek, MSD). The projected number of cases of multiple sclerosis to be recruited in the next 3 years is 75 (with 26 identified from February to July 2008), but it is too early to confirm either the number of cases that can be recruited within 3 years or the time required to perform a meaningful analysis [43]. Table Thirty Three (page 104) summarises the target number of cases to be recruited in 3 years for the various conditions. The Panel believes this is too uncertain given the serious nature of MS and the lack of evidence at present. Given that a large scale vaccination program has already been underway in Australia for 18 months and given the existing infrastructure associated with ongoing MS epidemiological surveillance, it is postulated that such a study should and could be conducted more quickly using Australian data.

One option would be a study in the metropolitan Melbourne and Sydney regions that includes both retrospective and prospective case ascertainment. Subject to ethics committee approval, case ascertainment could occur through a review of both clinical and radiological sources. Each case would then be interviewed to obtain data on a range of factors related to demyelination risk, including immunisation history, which would be verified from records. In this way, it would be possible to determine whether the total number of cases with a temporal association with Gardasil administration does not exceed that expected to occur by chance. Should previously undetected cases temporally related to Gardasil be identified, the pattern of these could be the subject of a more formal epidemiological assessment.

7.2 Recommended ongoing surveillance and risk minimisation activities

The Panel recommends that:

1. All reports of an association between Gardasil and demyelinating disorders continue to be monitored via the current spontaneous reporting mechanism to the TGA's Adverse Drug Reactions System database.

2. Enhanced active surveillance is required to identify all possible cases of demyelinating disorders in a defined at-risk population, as it is well known that reporting through the passive surveillance systems is usually incomplete. This should include an active audit of cases of demyelinating events in a defined population, commencing in 2009, with results reviewed at least quarterly. Such surveillance

[42] The PGRx System® is a commercial database developed by the ALPHA Network company for the purpose of conducting pharmacoepidemiological studies for regulatory and research purposes. The PGRx system systematically collects cases of a number of different adverse events and pools of potential controls. Exposure to drugs in cases and referents is ascertained through guided telephone interviews and computerized prescription records (from physicians or pharmacists). Relative risks are estimated through the computation of odds ratios. The system is fully implemented in France and currently undergoing implementation in Canada and Belgium.
[43] Assuming a prevalence of exposure to Gardasil between 10 to 40% controls, a matched case control study with a 1:4 case-control ratio and a one-sided 0.5 level of α and a statistical power of 80%, minimal detectable odds ratios can be calculated. With 30-75 cases targeted for most condition, the minimal detectable odds ratio ranged from 2 to 6.

would generate more accurate information about the incidence of demyelinating disorders and facilitate investigation of cases following Gardasil vaccination. It is recommended that the Panel be asked to endorse the final design and protocol for the surveillance activity.

3. If enhanced surveillance identifies a reason for concern, additional studies, such as case-control studies, would be warranted to further evaluate the validity and statistical significance of the observed association between Gardasil vaccine and the onset or exacerbation of demyelinating disorders. It is recommended that the Panel be asked to endorse the final design and protocol of any such study.

4. Any future large scale vaccination programs, especially those involving new vaccines, should have appropriate risk management strategies, including active surveillance mechanisms, established before commencement.

7.2.1 Should patients with autoimmune disease and, specifically, MS receive Gardasil?

There is no scientific evidence at this stage to treat Gardasil any differently to other vaccines for patients with existing autoimmune disease and specifically multiple sclerosis. Current accepted practice amongst neurologists is summarised in McAlpine's Multiple Sclerosis[44], based on a comprehensive review of the literature pertaining to the association of vaccination and both the onset of multiple sclerosis and relapse of multiple sclerosis, with particular focus on hepatitis B vaccination:

> *"Vaccinations in general and hepatitis B vaccination in particular are not a risk factor for the onset or relapse of multiple sclerosis. The most plausible explanation for the reported examples is coincidence not causality. Therefore there is* ***no reason to advise****:*
> - *people with multiple sclerosis to avoid vaccinations including hepatitis B: it makes sense to wait for a relatively silent period of the disease, free from relapse for 12 months and patients receiving immunosuppressive drugs should have a higher threshold for avoiding vaccinations with living components*
> - *relatives of patients with multiple sclerosis, notably children to avoid vaccinations, hepatitis B included*
> - *the general population to avoid hepatitis B vaccination".* [45]

8 Post script

A cut off date of 31 October 2008 was chosen for this review to allow sufficient time for the assessment and investigation of reports by the TGA and to allow timely consideration by the Panel of the nature and number of adverse event reports, and their significance in terms of the overall safety of Gardasil.

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[44] Compston A, Confavreux C, Lassmann H, et al (eds) 2006. McAlpine's Multiple Sclerosis. Philadelphia; Churchill Livingstone. Page 268.

[45] The accepted position is endorsed by the American Academy of Neurology, the Institute of Medicine of the USA, the World Health Organisation; Global Advisory Committee on Vaccine Safety and the Agence Francaise de Securite Sanitaire des Produits de Sante, among others.

In the period 1 November 2008 to 31 January 2009, the TGA received a further 61 reports of suspected adverse drug reactions to Gardasil. Reports of particular interest are summarised below, noting that some are still undergoing active investigation by the TGA's OMSM and their significance will need to be assessed more fully when the investigations are complete[46]:

- A single report (ADRS No. 246080) from a specialist in Queensland of optic neuritis in a 22 year old woman who presented with foggy vision and colour disturbances in her right visual field associated with right eye pain 80 days after her second dose of Gardasil. The latency of this particular event is outside the recognised window of biological plausibility;

- A single additional report of pancreatitis (ADRS No. 246348) in a 24yr old woman. This patient was experiencing abdominal pain prior to her 3rd injection of Gardasil. The pain worsened after the injection, requiring hospitalisation and opiate analgesia. She was subsequently found to have elevated serum amylase (656U/L) and lipase (1743U/L). No cause of the pancreatitis has been found, although viral serology results are still being pursued and the patient's serum lipid profile appears not to have been assessed. It was noted the patient had been on the OCP since 2004; and

- There were two new reports of disease of possible autoimmune aetiology:
  - One case (ADRS No. 247555) of SLE in a 22 yr old woman presenting with arthritis, myalgia and fatigue post first dose. Symptoms markedly worsened after the second dose and she was found to be strongly ANA seropositive; and
  - One case of possible autoimmune haemolytic anaemia was reported (ADRS No. 246254). A 13 yr old girl presented 8 days post 1st dose of Gardasil with jaundice and unconjugated hyperbilirubinaeamia. She was anaemic and had concurrent neutropenia (suggestive of a possible infective cause) and the exact cause is unclear.

The Panel considers these additional reports do not affect its overall conclusions.

[46] The TGA also received a single report of multiple sclerosis from NSW Health (ADRS No. 247741), however this was found to be a duplicate of an earlier report from them (ADRS No. 242796). A report of idiopathic thrombocytopaenic purpura (ADRS No. 247557) was also received, however specific mention was made of viral and autoimmune screens having been negative (see also footnote to Table Nineteen, page 75).

Part B

Tables and Figures

TABLE ONE Efficacy of Gardasil – key clinical study results reviewed ahead of marketing approval

Population	Gardasil		Placebo		% Efficacy (95%CI)	
	n	Number of cases	n	Number of cases		
HPV 16- or 18-related CIN 2/3 or AIS						
Protocol 005*	755	0	750	12	100.0	(65.1 - 100.0)
Protocol 007	231	0	230	1	100.0	(<0 - 100.0)
FUTURE I (013)	2200	0	2222	19	100.0	(78.5 - 100.0)
FUTURE II (015)	5301	0	5258	21	100.0**	(80.9 - 100.0)
Combined protocols	**8487**	**0**	**8460**	**53**	**100.0****	**(92.9 - 100.0)**
HPV 6-, 11-, 16-, 18-related CIN (CIN1, CIN2/3) or AIS						
Protocol 007	235	0	233	3	100.0	(<0 - 100.0)
FUTURE I (013)	2240	0	2258	37	100.0**	(89.5 - 100.0)
FUTURE II (015)	5383	4	5370	43	90.7	(74.4 - 97.6)
Combined protocols	**7858**	**4**	**7861**	**83**	**95.2**	**(87.2 - 98.7)**
HPV 6-, 11-, 16-, 18-related Genital lesions (Genital warts, VIN, VaIN)						
Protocol 007	235	0	233	3	100.0	(<0.0 - 100.0)
FUTURE I (013)	2261	0	2279	40	100.0**	(90.3 - 100.0)
FUTURE II (015)	5401	1	5387	70	98.6	(91.8 - 100.0)
Combined protocols	**7897**	**1**	**7899**	**113**	**99.1**	**(95.0 - 100.0)**

* Evaluated only the HPV 16 L1 VLP vaccine component of Gardasil.
** p-values were computed for pre-specified primary hypothesis tests. All p values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE I); efficacy against HPV 16/18-related CIN 2/3 is >25% (Combined protocols); efficacy against HPV 6/1//16/18-related CIN is >20% (FUTURE I); and efficacy against HPV 6/11/16/18-related external genital lesions (EGL) is >20% (FUTURE I).
n= number of subjects with at least one follow-up visit after Month 7.
Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

TABLE TWO Status of post marketing commitments for Gardasil

Commitment/requirement	Status
Final study reports 013, 015	Submitted to TGA as part of 2008 application for extension of indication (EOI) (see Section 2.3)
Long term follow up from Nordic Registry	1st interim report due mid 2009. Reports expected every 5 years until first breakthrough case
Long term immunity data from protocol 018-06	Data to month 30 follow-up submitted with 2008 application for EOI. Further follow-up reports expected (see Section 2.3)
Long term safety data from protocol 018-05	Data to month 30 follow-up submitted with 2008 application for EOI. Further follow-up reports expected (see Section 2.3)
Efficacy data for 16 to 26 year old males	Will be submitted as part of an application for EOI to include male genital warts – expected to occur in Feb 2009. The application will include updated information for current indication in males, which is based on immunogenicity bridging study
Annual reports from US pregnancy registry	Submitted to TGA as part of 2008 application for extension of indication (EOI) (see Section 2.3)
MCO surveillance study	Not a formal TGA requirement but MSD expects to submit interim reports to TGA as they become available

TABLE THREE Updated prophylactic efficacy of Gardasil – as per current approved PI

Population	Gardasil		Placebo		% Efficacy (95%CI)	
	n	Number of cases	n	Number of cases		
HPV 16- or 18-related CIN 2/3 or AIS						
Protocol 005	755	0	750	12	100.0	(65.1 - 100.0)
Protocol 007	231	0	230	1	100.0	(<0 - 100.0)
FUTURE I (013)	2201	0	2222	30	100.0	(86.9 - 100.0)
FUTURE II (015)	5305	1*	5258	42	97.6	(86.2 - 99.9)
Combined protocols	**8492**	**1***	**8460**	**85**	**98.8**	**(93.3 - 100.0)**
HPV 16- or 18-related VIN 2/3						
Protocol 007	231	0	230	0	Not calculated	
FUTURE I (013)	2219	0	2239	4	100.0	(<0 - 100.0)
FUTURE II (015)	5321	0	5237	4	100.0	(<0 - 100.0)
Combined protocols	**7771**	**0**	**7742**	**8**	**100.0**	**(41.7 - 100.0)**
HPV 16- or 18-related VaIN 2/3						
Protocol 007	231	0	230	0	Not calculated	
FUTURE I (013)	2219	0	2239	3	100.0	(<0 - 100.0)
FUTURE II (015)	5321	0	5237	4	100.0	(<0 - 100.0)
Combined protocols	**7771**	**0**	**7742**	**7**	**100.0**	**(30.9 - 100.0)**
HPV 6-, 11-, 16-, 18-related CIN (CIN1, CIN2/3) or AIS						
Protocol 007	235	0	233	3	100.0	(<0 - 100.0)
FUTURE I (013)	2241	0	2258	65	100.0	(94.2 - 100.0)
FUTURE II (015)	5387	6**	5372	80	92.6	(83.1 - 97.4)
Combined protocols	**7863**	**6****	**7863**	**148**	**96.0**	**(91.0 - 98.5)**
HPV 6-, 11-, 16-, 18-related Genital lesions (Genital warts, VIN, VaIN, vulvar and vaginal cancer)						
Protocol 007	235	0	233	3	100.0	(<0.0 - 100.0)
FUTURE I (013)	2261	0	2279	60	100.0	(93.7 - 100.0)
FUTURE II (015)	5403	2	5387	126	98.4	(94.2 - 99.8)
Combined protocols	**7899**	**2**	**7899**	**189**	**99.0**	**(96.2 - 99.9)**
HPV 6- or 11-related Genital warts						
Combined protocols	**6931**	**2**	**6854**	**156**	**98.7**	**(95.4 - 99.8)**

* One case of CIN 3 where HPV 16 and 52 detected. Individual was chronically infected with HPV 52 (infection at day 1 and months 32.5 and 33.6) in 8 of 11 specimens including tissue that was excised during Loop Electro-Excision Procedure (LEEP). HPV 16 was found in 1 of 11 specimens at month 32.5 but not in tissue that was excised during LEEP. Base on virologic evidence the causal attribution is more likely to be HPV 52.

** One case of CIN 1, where HPV 18 and 56 were detected. Subject was infected with HPV 52 at enrolment and was diagnosed with cervical disease on biopsy (positive for HPV 52) and underwent LEEP. Biopsy and 2 of 4 LEEP specimens were positive for HPV 52. Only 1 specimen was positive for HPV 18.

TABLE FOUR Prophylactic efficacy of Gardasil – March 2008 submission

Population	Gardasil		Placebo		% Efficacy (95%CI)	
	n	Number of cases	n	Number of cases		
HPV 16- or 18-related CIN 2/3 or AIS						
Protocol 005	755	0	750	12	100.0	(65.1 - 100.0)
Protocol 007	231	0	230	1	100.0	(<0 - 100.0)
FUTURE I (013)	2201	0	2222	62	100.0	(93.9 - 100.0)
FUTURE II (015)	5306	2*	5262	63	96.9	(88.2 - 99.6)
Combined protocols	**8493**	**2***	**8464**	**112**	**98.2**	**(93.5 – 99.8)**
HPV 16- or 18-related VIN 2/3						
Protocol 007	231	0	230	0	Not calculated	
FUTURE I (013)	2219	0	2239	6	100.0	(14.4 - 100.0)
FUTURE II (015)	5322	0	5275	4	100.0	(<0 - 100.0)
Combined protocols	**7772**	**0**	**7744**	**10**	**100.0**	**(55.5 - 100.0)**
HPV 16- or 18-related VaIN 2/3						
Protocol 007	231	0	230	0	Not calculated	
FUTURE I (013)	2219	0	2239	5	100.0	(<0 - 100.0)
FUTURE II (015)	5322	0	5275	4	100.0	(<0 - 100.0)
Combined protocols	**7772**	**0**	**7744**	**9**	**100.0**	**(49.5 - 100.0)**
HPV 6-, 11-, 16-, 18-related CIN (CIN1, CIN2/3) or AIS						
Protocol 007	235	0	233	3	100.0	(<0 - 100.0)
FUTURE I (013)	2241	0	2258	77	100.0	(95.1 - 100.0)
FUTURE II (015)	5388	9**	5374	145	93.8	(88.0 - 97.2)
Combined protocols	**7864**	**9****	**7865**	**225**	**96.0**	**(92.3 - 98.2)**
HPV 6-, 11-, 16-, 18-related Genital lesions (Genital warts, VIN, VaIN, vulvar and vaginal cancer)						
Protocol 007	235	0	233	3	100.0	(<0.0 - 100.0)
FUTURE I (013)	2261	0	2279	74	100.0	(94.9 - 100.0)
FUTURE II (015)	5404	2	5390	150	98.7	(95.2 - 99.8)
Combined protocols	**7900**	**2**	**7902**	**227**	**99.1**	**(96.8 - 99.9)**

* Two cases of CIN 3. In the first case HPV 16 and 52 detected. This individual was chronically infected with HPV 52 (infection at day 1 and months 32.5 and 33.6) in 8 of 11 specimens including tissue that was excised during Loop Electro-Excision Procedure (LEEP). HPV 16 was found in 1 of 11 specimens at month 32.5 but not in tissue that was excised during LEEP. Base on virologic evidence the causal attribution is more likely to be HPV 52. In the second case HPV 16, 51 and 56 were detected. This individual was infected with HPV 51 (detected by PCR on day 1) in 2 of 9 specimens. HPV 56 was detected in tissue excised during LEEP in 3 of 9 specimens at month 52. HPV 16 was detected in 1 of 9 specimens at a month 51 biopsy. Given that these cases occurred in the context of a mixed infection with the dominant type being the non-vaccine type, it is likely that the relevant vaccine type was not the causal HPV type, in which case vaccine efficacy against HPV 16/18-related CIN2/3 or AIS would be 100%.

** Among 9 cases of HPV 6, 11, 16 or 18 related CIN (any grade) or AIS detected, 6 cases are likely to be due to a non-vaccine HPV type and not to a vaccine HPV type.

TABLE FIVE New medical conditions potentially indicative of autoimmune phenomena arising in the Gardasil clinical trial program (protocols 007, 013, 015, 016, 018 and 019)

	Gardasil* n = 13686	**Placebo** n = 11588
Subjects with one or more new medical conditions	9731 (71.1%)	8487 (73.2%)
Hypothyroidism	47 (0.3%)	55 (0.3%)
Arthritis	14 (0.1%)	12 (0.1%)
Psoriasis	12 (0.1%)	14 (0.1%)
Hyperthyroidism	12 (0.1%)	12 (0.1%)
Goitre	11 (0.1%)	11 (0.1%)
Coeliac Disease	10 (0.1%)	6 (0.1%)
Arthropathy	7 (0.1%)	0
Rheumatoid arthritis	7 (0.1%)	2 (0.0%)
Autoimmune thyroiditis	6 (0.0%)	1 (0.0%)
Basedow's Disease	5 (0.0%)	2 (0.0%)
Crohn's Disease	4 (0.0%)	3 (0.0%)
Ulcerative colitis	3 (0.0%)	3 (0.0%)
Insulin dependent diabetes mellitus	3 (0.0%)	2 (0.0%)
Alopecia areata	3 (0.0%)	3 (0.0%)
Erythema nodosum	3 (0.0%)	4 (0.0%)
Uveitis	3 (0.0%)	1 (0.0%)
Pigmentation disorder	3 (0.0%)	1 (0.0%)
Raynaud's phenomenon	3 (0.0%)	4 (0.0%)
Thyroiditis	2 (0.0%)	0
Inflammatory bowel disease	2 (0.0%)	2 (0.0%)
Juvenile arthritis	2 (0.0%)	2 (0.0%)
Morphoea	2 (0.0%)	0
Multiple sclerosis	2 (0.0%)	4 (0.0%)
Optic neuritis	2 (0.0%)	0
Vitiligo	2 (0.0%)	1 (0.0%)

* The following conditions were also observed in a single patient in the Gardasil group (the number of patients with each condition in placebo group are shown in brackets): autoimmune thrombocytopenia (0), toxic nodular goitre (1), iritis (2), ulcerative proctitis (0), antiphospholipid syndrome (1), sarcoidosis (0), ankylosing spondylitis (1), reactive arthritis (1), psoriatic arthropathy (1), sacroiliitis (0), Sjogren's syndrome (0), SLE (3), glomerulonephritis minimal lesion (0), nephritis (4), pemphigus (0), Stevens-Johnson Syndrome (0) and vasculitis (0).

TABLE SIX Pregnancy outcome data from Gardasil Phase III clinical trials

	Gardasil	**Placebo**
Number (%) subjects with pregnancy	1796 (14.6%)	1824 (16.5%)
Number of pregnancies	2085	2121
Number of pregnancies with known outcome	2008	2029
Number (%) of live births	1447 (72.1%)	1424 (70.2%)
Number (%) of foetal loss	559 (27.8%)	602 (29.7%)
Number (%) of infant/foetal congenital anomaly	40 (2.8%)	30 (2.1%)
Live birth with diagnosis made in neonatal period	30	22
Live birth with diagnosis made after neonatal period	3	2
Live birth with diagnosis *in utero*	5	3
Foetal loss	2	3

TABLE SEVEN Spontaneous Gardasil ADR reports by System Organ Class with frequent reaction terms

Disorder (System Organ Class)	Number of reactions (% of total reaction terms)	Frequent reactions (number)
General disorders and administration site conditions	644 (18.6)	Injection site reactions (255), Body temperature increased (137), Malaise (100), Fatigue (56), Pain (33)
Nervous system	616 (17.8)	Headache (244), Dizziness (172), Syncope (110), Lethargy (68), Paraesthesia (59)
Skin and subcutaneous tissue	459 (13.2)	Rash (193), Urticaria (107), Erythema (35), Hyperhidrosis (29), Face oedema (13)
Gastrointestinal	349 (10)	Nausea (195), Vomiting (94), Abdominal pain (61), Diarrhoea (25), Tongue/mouth disorder (24)
Vascular	327 (9.4)	Pallor (40), Flushing (25)
Cardiac	319 (9.2)	Palpitations (11), Tachycardia (7), Bradycardia (2)
Musculoskeletal and connective tissue	177 (5.1)	Myalgia (46), Arthralgia (28) , Muscular weakness (21), Back pain (16)
Psychiatric	174 (5)	Anxiety (9), Insomnia (9)
Immune system	172 (4.9)	Anaphylaxis (14), hypersensitivity (7)
Respiratory, thoracic and mediastinal	135 (3.8)	Dyspnoea (38), Throat tightness (22), Oropharyngeal pain (17)
Eye	72 (2)	Vision disorder (38), Ocular allergic reaction/oedema (16), Photophobia (9)
Metabolism and nutrition	60 (1.7)	Anorexia (21)
Blood and lymphatic system	39 (1.1)	Lymphadenopathy/ lymphadenitis (26), Eosinophilia (10)
Reproductive system and breast	34 (0.9)	Menstrual disorder (10), Vulvo-vaginal reaction (13)
Infections and infestations	33 (0.9)	Respiratory tract infection (10), Herpes simplex infection (6)
Investigations	18 (0.5)	
Ear and labyrinth	13 (0.4)	Vertigo (5), Tinnitus (2), Ear pain (2), Deafness (2)
Renal and urinary	13 (0.4)	Urinary incontinence (6)
Injury, poisoning and procedural complications	10 (0.3)	
Endocrine	9 (0.25)	Hypophysitis (1), Goitre (1)
Pregnancy, puerperium and perinatal conditions	5 (0.14)	
Hepatobiliary	3 (0.1)	Hepatic function abnormal (2), Hepatitis (1)
Neoplasms benign, malignant and unspecified	3 (0.08)	
Surgical and medical procedures	2 (0.05)	
Social circumstances	1 (0.02)	

TABLE EIGHT VSD RCA Study Outcomes

Outcome	Exposure window (days)	Medical setting	First in what period?
Guillain Barré Syndrome	1 to 42	All	42 days
Seizures	0 to 42	Inpatient, ED	42 days
Syncope	0	All	2 days
Stroke	0 to 42	Inpatient, ED	42 days
Venous thromboembolism	1 to 42	All	1 year
Appendicitis	0 to 42	Inpatient, ED	42 days
Anaphylaxis	0 to 2	All	2 days
Other allergic reactions	0 to 2*	All	42 days

EDEmergency department
* exclude day 0 if clinic setting

TABLE NINE VSD RCA Study Results – Preliminary analysis

Historical comparisons

Outcome	Events observed	Events expected	RR	Log Likelihood Ratio (LRR)*	Critical Value of LRR	Signal?
Guillain Barré Syndrome						
Adults	0	0.31	0.00	0.00	2.86	No
Youths	0	0.50	0.00	0.00	2.86	No
Appendicitis						
Adults	21	21.12	0.99	0.00	3.68	No
Youths	33	41.99	0.79	0.00	3.86	No
Stroke						
Adults	3	1.58	1.91	0.51	2.97	No
Youths	0	0.84	0.00	0.00	2.97	No
Venous thromboembolism						
Adults	7	10.11	0.69	0.00	3.57	No
Youths	7	3.57	1.96	1.28	3.25	No

* LRR is automatically set to zero when RR < 1

Concurrent comparisons

Outcome	Exposed cases	Unexposed cases	Comparison visit	RR	Binomial Test p-Value	Threshold p Value	Signal?
Seizure							
Adults	18	26	PC	1.18	0.39	0.02	No
Youths	34	14		1.13	0.45	0.02	No
Syncope							
Adults	129	57	Vacc	0.54	0.99	0.03	No
Youths	452	120		0.99	0.56	0.04	No
Other allergic reactions							
Adults	32	7	Vacc	1.45	0.26	0.02	No
Youths	44	24		0.75	0.85	0.02	No

PC = preventative care visits – for adults 211,878 and for youths 141,329
Vacc = vaccination visits – for adults 34,917 and for youths 106,252

TABLE TEN VSD RCA Study Syncope Logistic Regression Results (Concurrent comparison group)

	Age and secular trend adjustment*		
	RR	**95%CI**	**p Value**
Youth (9-17yrs)	0.99	0.80 – 1.22	0.93
Adults (18 – 26yrs)	0.66	0.48 – 0.91	0.01
Combined (9 – 26yrs)	0.88	0.74 – 1.05	0.16

* Age adjusted by 2-3 year age groups: 9-10, 11-12, 13-14, 15-17, 18-19, 20-21, 22-23, 24-26

TABLE ELEVEN Gardasil - Confirmed Australian cases of anaphylaxis

	ADRS No.	**Brighton***	**State**	**Dose**	**Treatment; outcome**
1	228973	level 2	NSW	n/a	adrenaline; hospital; recovered
2	228978	level 3	NSW	1	hospital; recovered
3	229316	level 3	NSW	n/a	adrenaline; hospital; recovered
4	229318	level 2	NSW	1	adrenaline; hospital
5	229918	level 3	NSW	2	adrenaline; hospital; recovered
6	230515	level 2	WA	n/a	adrenaline; hospital; recovered
7	230560	level 2	NSW	2	adrenaline; hospital; recovered
8	230754	level 2	VIC	2	antihistamine; hospital
9	231983	level 2	NSW	1	adrenaline; hospital; recovered
10	232965	level 2	WA	1	adrenaline; hospital
11	234818	level 2	Qld	3	visit to GP; adrenaline; phenergan; cortisone; recovered
12	244630	level 2	NSW	n/a	adrenaline; ventolin; hospital; prednisone; recovered
13	244642	level 2	NSW	n/a	adrenaline; hospital; prednisone; recovered

*Classification according to the Brighton Collaboration case definition of anaphylaxis

TABLE TWELVE Summary statistics - spontaneous Gardasil ADR reports of urticaria

	State or Territory									
	Total	**NSW**	**Vic**	**Qld**	**WA**	**SA**	**Tas**	**ACT**	**NT**	**Unk***
Total no. reports of urticaria	**107**	35	35	7	8	10	3	4	2	3
Rate per million doses distributed	23.7	23.4	29.2	8.0	18.1	37.8	28.7	47.6	39.2	NA
Reports of urticaria from Health Department	82	30	30	3	5	9	0	3	2	
a. Initial report made by medical professional or institution	19^	2	9^	2^	1	3		1	1	
b. Initial report made by nursing/immunisation professional	9		5	1	2	1				
c. Initial report made by patient, relative or other individual	24		16		1	5		2		
c1. With evidence of medical review having occurred	*6*		*3*			*2*		*1*		
c2. With no evidence of medical review having occurred	*18*		*13*		*1*	*3*		*1*		
d. Unclear source	30	28			1				1	
d1. With evidence of medical review having occurred	*17*	*17*								
d2. With no evidence of medical review having occurred	*13*	*11*			*1*				*1*	
e. Reports of urticaria from medical professional or institution	21^	5	5	4	2	1	3^	1		
f. Reports of urticaria from other sources	4				1					3
Total no. reports of "medically confirmed" urticaria *(a+e)*	**37****	7	13**	5**	3	4	2**	2	1	0
Rate per million doses distributed	8.21	4.68	10.83	5.74	6.82	15.14	19.14	23.8	19.58	NA
Total no. reports of urticaria where medical attention received *(a+c1+d1+e)*	63	24	16**	6	3	6	2**	3	1	0
Rate per million doses distributed	13.98	16.07	13.33	6.88	6.82	22.7	19.14	35.7	19.58	NA
Total no. reports of "confirmed" anaphylaxis (see Table Two)	**13**	9	1	1	2	0	0	0	0	0
Rate per million doses distributed	2.88	6.03	0.83	1.14	4.55	0	0	0	0	NA

* Reports through Adverse Medicine Event Line ^ Includes a single report based on history alone ** Adjusted for GP reports where it was stated rash

was not observed – i.e. report based on history alone

(see ^)

TABLE THIRTEEN Australian Gardasil ADR reports with reaction terms MS, transverse myelitis, CNS inflammation/lesion, optic neuritis

ADRS No.	Vacc Year	State/Locat'n (1^0 reporter)	Age	Diagnosis/clinical features	Dose	Latency	Meets case def'n?	MSD WAES No.	Comment
236306 *	2007	NSW/Sydney (Neurologist)	22	**CDMS**. Headache, transverse myelitis and optic neuritis. Prior episode of optic neuritis and abn. MRI	2	1 day	Y	0711AUS00143	Patient diagnosed with CDMS after the second attack following immunisation
242785 *	2008	NSW/Sydney (Neurologist)	26^	**CDMS**. Sensory disturbance L leg with multiple demyelinating brain lesions on MRI. 4 years prior had episode of paraesthesia	3	4 days	Y		Classified as CDMS on basis of McDonald criteria - 2 separate clinical episodes and MRI changes
242789 *	2007	NSW/Sydney (Neurologist)	16	**CDMS**. Features consistent with R brain stem lesion, confirmed by MRI. 61/2 months prior had episode of ataxia, diplopia and spinal syndrome (diagnosed as ADEM).	2	4 days	Y		Classified as CDMS on basis of McDonald criteria - 2 separate clinical episodes and MRI changes
242793 *	2007	NSW/Sydney (Neurologist)	16	**CIS** (FDE). R hand clumsiness, marked sensory loss and pseudoathetosis	3	21 days	Y		Multiple brain lesions on MRI, with cervical spine lesion clearly responsible for clinical signs
242796 *	2007	NSW/Sydney (Neurologist)	25	**CIS** (FDE). Initially presented with R hemiplegia, dysarthria, oligoclonal bands in CSF. Four months later developed R leg paraesthesia with new brain lesion on MRI	2	16 days	Y	0807AUS00041	Subsequently gone on to develop CDMS
234408	2007	NSW/Sydney (Ophthalmologist)	24	**Acute macular retinopathy** (an autoimmune retinopathy). **Viral URTI.** Blurred vision L>R associated with scotoma. Had preceding viral URTI (at same time as vaccination).	NR	28 days	N	0805AUS00033	Viral infection is known to be associated with AMN and is the most likely precipitant in this case. Note: AMN is not a demyelinating disorder
237812	2007	ACT (Neurologist)	16	**CDMS**. R sided numbness which recovered, 3 weeks later R optic neuritis. Several lesions on MRI.	2	63 days	N	0801AUS00163	Latency too long for causal association
243264	2007	Vic (Parent)	17	**CDMS**. Descending sensory loss. Transverse myelitis and optic neuritis.	1	7 days	Y	0808AUS00036	Treating neurologist confirmed clinical details and diagnosis
244364	2008	NSW (Neurologist)	26	**Optic neuritis**, migrainous headache. Mild "decrease in vision". MRI brain and orbits – increased signal intensities within periventricular white matter. Optic nerves appear unremarkable.	1	Within 21 days	Y		Finding of white matter lesions on MRI increases risk that patient will progress to MS at some time in future. **CIS**

Shading denotes cases of confirmed demyelination occurring within 6 weeks of vaccination. * Barnett and Sutton cases

^ Two (initial and follow-up) ADR reports received from NSW Health had different ages – 16 and 26. Draft paper by Sutton et al recorded the age as 16, but the final printed article (presumably after proof reading by the authors) stated the age was 26 years.

TABLE FOURTEEN **Australian Gardasil ADR reports with reaction terms acute disseminated encephalomyelitis, encephalomyelitis, leukoencephalomyelitis or encephalitis**

ADRS No.	Vacc Year	State/Locat'n (1^0 reporter)	Age	Diagnosis/clinical features	Dose	Latency	MSD WAES No.	Comment
235453	2007	NSW/Sydney (Hospital RMO)	17	**ADEM**. Agitation, confusion, ataxia. MRI consistent with ADEM	2	82 days		Low biological plausibility due to long period between vaccination and onset of ADEM
243038	2007	Vic (Neurologist)	21	**ADEM** in patient with RRMS. Personality change, headache, seizures and altered consciousness.	2	28 days		Unusual to develop ADEM in the course of RRMS. Suspicious case
243040	2008	NSW/Central coast (G.P)	26	**?Viral Encephalitis**. Severe headache, vomiting	1	Same day		Patient declined LP. **Diagnosis uncertain**

Shading denotes case of confirmed demyelination occurring within 6 weeks of vaccination.

TABLE FIFTEEN Australian Gardasil ADR reports with reaction terms neuropathy, peripheral neuropathy, Guillain Barré Syndrome

ADRS No.	Vacc Year	State/Locat'n (1^0 reporter)	Age	Diagnosis/clinical features	Dose	Latency	MSD WAES No.	Comment
233239	2007	WA/Perth (Physician)	16	**Chronic inflammatory demyelinating polyneuropathy**. **Mycoplasma infection** Numbness of feet followed by bilateral foot drop two weeks later. Diagnosis changed from GBS to CIDP on basis of worsening condition and NCS.	2	43 days		6 weeks prior to onset of neurological symptoms and for two weeks after them patient had a febrile illness with positive Mycoplasma titre which rose and later fell, consistent with Mycoplasma infection. Mycoplasma has been associated with GBS and is the more likely precipitant in this case
234391	2007	Qld (Physician)	16	**No organic disease**. Bilateral ascending sensory loss both lower limbs. No weakness and normal reflexes. NCS normal	2	27 days		Thought by neurologist not to be GBS.
235044	2007	Vic/Melbourne (Neurologist)	17	**Guillain Barré Syndrome**. Progressive weakness in upper and lower limbs, fatigue in absence of preceding viral illness. NCS consistent with GBS.	2	14 days		
243347	2008	Qld (Patient)	25	**Pleurisy**. Paralysis L side, pleuritic chest pain and difficulty breathing. Also developed fatigue, weakness and incoordination. **Self diagnosed GBS**	1	2 days	0807AUS00099	Not consistent with GBS which is symmetrical, bilateral ascending neuropathy. Neurological review failed to confirm a diagnosis. MRI and blood tests normal. Report has since been amended to remove the term 'Guillain Barré Syndrome'

246157	2008	Qld/Cairns (Paediatrician)	15	**Muscle weakness, hyperreflexia, paraesthesia** Bilateral ascending weakness in lower limbs to knee level. Tingling in upper extremities. Admitted to hospital with **?Guillain Barré Syndrome**. Decreased lower limb power (R>L) on examination with hyperreflexia. Sensation intact. CSF normal. Elevated anti-Ganglioside GM1 IgG (14; NR<10) and IGM (93; NR <15). Throat swabs and faecal specimens clear of pathogens.	3	1 day		Had chest infection 2 weeks prior to admission, treated with Augmentin. No NCS performed. Areflexia not a feature of this case and no neurological level established. No definitive diagnosis made.

Shading denotes case of confirmed demyelination occurring within 6 weeks of vaccination.

TABLE SIXTEEN Gardasil - Miscellaneous Australian neurological reports reviewed by Panel neurologists

ADRS No.	Vacc Year	State/Locat'n (1^0 reporter)	Age	Diagnosis/clinical features	Dose	Latency	MSD WAES No.	Comment
230073	2007	Vic (Physician)	16	**Brachyneuritis** Numbness and pain at injection site, spreading to hand and down leg. Leg symptoms resolved over one day. Over next 5 days unable to move arm. MRI showed evidence of neuritis of C5, C6 and C7 nerve roots but NCS normal. Paediatrician diagnosed conversion type disorder. Physician considered patient to have complex regional pain syndrome	1	Same day	0705AUS00191	Brachyneuritis has been associated with vaccination
237037	2007	Vic (Paediatric Registrar)	17	**No serious CNS pathology**. Pain in L arm followed three days later by L arm paralysis, paraesthesia and then L sided face, arm and leg weakness. MRI normal	3	1 day		Inconsistent clinical findings

242877	2008	NT/Darwin (Infectious Diseases Registrar)	13	Headache, abn behaviour. Cerebellar signs. Cerebellitis on MRI **Acute cerebellitis**	1	14 days		**US Citizen, vaccinated in USA.** Clinical picture of ADEM with MRI evidence of inflammation of the cerebellum.

Shading denotes case of confirmed demyelination occurring within 6 weeks of vaccination.

TABLE SEVENTEEN Australian Gardasil ADR reports with reaction terms ataxia, paresis, hemiparesis, monoparesis, palsy or paralysis

ADRS No. (1^0 reporter)	Reaction terms	Clinical description	Assessment on triage within OMSM
228981 (Community nurse)	Bell's **palsy**	2 days post dose woke with swollen cervical glands on R side (opposite side to injection site) and red itchy swollen R eyelid. Complained of drooped face and associated loss of sensation. L eyelid then became swollen. Generally unwell, sleepy.	Sensory disturbance not a feature of Bell's palsy which is purely lower motor neurone disorder. Features more suggestive of allergic type reaction.
228995 (Physician)	Aphasia, Dizziness, Facial **paresis**, Fatigue, Headache, Hypoventilation Muscular weakness, Neuropathy peripheral, Somnolence, Syncope	On day of first dose collapsed complaining of weakness in limbs and face, headache and dizziness. Later unable to speak, appeared drowsy. Hospitalised - no organic cause found. EEG and CT brain normal. Symptoms resolved in 48hrs. NOTE coded as ascending neuropathy on MSD report	Considered to be hysterical reaction on basis of timing of onset and recovery and normal investigations.
230073 (Physician)	Hyporeflexia, **Paralysis**, Injection site pain	Numbness and pain at injection site, spreading to hand and down leg. Leg symptoms resolved over one day. Over next 5 days unable to move arm. MRI showed evidence of neuritis of C5, C6 and C7 nerve roots but NCS normal. Paediatrician diagnosed conversion type disorder. Physician considered patient to have complex regional pain syndrome.	Referred to Panel neurologists (see Table Thirteen)
231773 (Paediatrician)	Injection site reaction, **Monoparesis**, Oedema, Skin discolouration	Onset of symptoms immediately after injection: weakness L arm, L arm pain, purplish discoloration, tender skin. Presumed regional pain syndrome.	Weakness and pain secondary to regional pain syndrome and local reaction to injection
235453 (Hospital RMO)	Agitation, **Ataxia**, Confusional state, Encephalitis	Agitation, confusion, ataxia. MRI consistent with ADEM	Identified through search no. 2. Referred to Panel neurologists (see Table Eleven)
235501 (G.P.)	Cranial nerve **paralysis**	R Bell's palsy 1 day post dose 3	Case of Bell's palsy
235727 (Medical centre)	Back pain, **Paralysis**	Patient reported feeling paralysed with severe back pain for 18 hours then settled	Scant information. No objective evidence of weakness
237037 (Paediatric Registrar)	Complex regional pain syndrome, **Hemiparesis**, Injection site pain, Pain in extremity, Paraesthesia, **Paralysis**	Pain in L arm followed three days later by L arm paralysis, paraesthesia and then L sided face, arm and leg weakness. MRI normal	Referred to Panel neurologists (see Table Thirteen)
237859 (G.P.)	Facial **paralysis**	R sided facial paralysis one day after first dose. Resolved over a few weeks. Past history of L sided Bell's palsy 3 months earlier	Likely Bell's palsy
238723 (Hospital pharmacist)	Facial **palsy**	"Patient experienced facial nerve palsy" a few weeks after second dose.	MSD report with minimal information.

TABLE SEVENTEEN c't'd Australian Gardasil ADR reports with reaction terms ataxia, paresis, hemiparesis, monoparesis, palsy or paralysis

ADRS No. (1^0 reporter)	Reaction terms	Clinical description	Assessment on triage
239356 (Paediatric Registrar)	Facial **palsy, Paresis**, Hyperventilation , Syncope	Immediate onset of hyperventilation, altered sensation, L arm weakness and facial weakness following immunisation. Bell's palsy confirmed 11 days later	Partial Bell's palsy said to have been confirmed in hospital E.D. Patient also received Boostrix (DTPa) vaccine.
240737 (Patient)	Dizziness, Fatigue, **Hemiparesis**	Weak R grip and weakness in R leg 24 hours post vaccination. Felt dizzy and tired. Recovered after 5 days	Scant information. No objective evidence of weakness
242789 (Neurologist)	Asthenia, Diplopia, Hypoaesthesia facial, **Monoparesis**, Transverse myelitis, Nausea, Vomiting	CDMS	Identified through search no. 1. Referred to Panel neurologists (see Table Ten)
242796 (Neurologist)	**Hemiparesis**, Lethargy Multiple Sclerosis	CIS	Identified through search no. 1. Referred to Panel neurologists (see Table Ten)
242877 (Infectious Diseases Registrar)	**Ataxia**, Dysarthria, Headache, Malaise, Mental impairment, Somnolence	Headache and abnormal behaviour with cerebellar signs	Referred to Panel neurologists (see Table Thirteen)
243168 (G.P.)	Bell's **palsy**, facial **palsy**	L sided facial palsy one month after vaccination (dose no. not reported). Recovered completely.	Case of Bell's palsy
243264 (Parent)	Multiple sclerosis, **Paresis**	Descending sensory loss. ?transverse myelitis and optic neuritis	Identified through search no. 1. Referred to Panel neurologists (see Table Ten)
244923 (G.P.)	Transient **paralysis**, Conversion reaction	In the evening of day of first dose patient woke to find she couldn't move her legs and had to crawl to the phone. Went back to bed and next morning was normal	Scant information. No objective evidence of weakness
245768 (Parent)	Numb lips, **facial palsy**, migraine	1 day after second dose had left facial droop associated with numb lips. Lasted 2 hours followed by a migraine. Subsequently had third dose without incident.	Parental report via NSW Health. No medical review at time of event. Patient also received varicella vaccine.

TABLE EIGHTEEN Summary of global reports to MSD with reaction terms Multiple Sclerosis and/or Optic neuritis

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
USA	Unk	**MS, Neurogenic bladder, Optic neuritis, Cognitive disorder** Bladder problems followed by optic neuritis and cognitive decline from Oct 07	Jul 07 (1)	Aug 07	4 weeks	Received four other vaccines concurrently. Report from physician. Minimal information. No diagnostic test results available. MSD has requested further information.	0808USA00236
	33	**MS** Diplopia, blurred vision MRI – hyperintensity along L pericollosal white matter and L parietal subcortical white matter AEP, VEP and BEPs normal	30 Apr 07 (?2)	30 Apr 07	Same day	Report from investigator engaged in GSK study of immunogenicity of Cervarix vs Gardasil. No further information expected by MSD. Same day onset has low biological plausibility but earlier dose given in Feb 07 (=8 weeks latency)	0712USA02491
	16	**Blurred vision, diplopia, optic neuritis** Acute onset of blurred vision L eye and diplopia for one day. MRI normal	29 Jan 07 (1)	8 Feb 07	10 days	Report from registered nurse. P't subsequently received 2nd dose in Apr 07 without incident. No further information expected by MSD.	0704USA00603
	16	**Blindness unilateral, headache, fatigue, papilloedema, optic neuritis** Headache, eye pain and loss of vision in one eye. MRI enlargement of L optic nerve	15 Mar 07 (1)	13 May 07	8 weeks	Received diphtheria and pertussis vaccines concomitantly. Report from physician. No further information expected by MSD.	0706USA01344
	12	**Optic neuritis, reduced VA, heterophoria, vision blurred** Severe eye pain on L gaze. Muddied colour vision, blurring of vision. Tenderness over L troclea. Visual fields – diffuse non specific loss L field VER normal. MRI Oct 07 Normal	8 Aug 07 (2)	11 Aug 07	3 days	Visual field loss thought to be functional. Report from physician. No further information expected by MSD.	0710USA04612
	16	**Paraesthesia, syncope, CNS lesion, vertigo, anxiety, pharyngolaryngeal pain, vomiting, cough, MS** Syncope sore throat, paraesthesia R & L hands, R toes. MRI multiple lesions in brain and lesion in cervical spinal cord. Repeat MRI Apr 08 new lesions.	8 May 07 (1)	15 May 07	7 days	History of paresthesia L hand, R forearm Nov 06. Physician report. MSD has requested further information.	0807USA00756

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
	29	**MS** Optic neuritis and sensory loss over half of body	Jul 07 (1) Sept 07 (2) Dec 07 (3)	Unk	Unk	Physician report. Minimal information. No diagnostic test results available. MSD has requested further information.	0805USA06228
	27	**Leukoencephalomyelitis, MS** Patient reported to have been hospitalised with acute MS and ADEM.	Aug 07 (1)	Sept 07	6 weeks	Physician report. Minimal information. No diagnostic test results available. MSD has requested further information.	0712USA01374
	16	**MS, cough, demyelination, hyperhidrosis, syncope, paraesthesia, hypoaesthesia, vomiting, fall, head injury** Vomiting, sweating and syncope. MRI multiple demyelinated foci in brain and cervical spinal cord.	8 May 07 (1)	14 May 07	6 days	History of numbness L thumb in Dec 06, spreading down hands and arms plus "funny feeling in lower back". Intermittent numbness since that time. Info obtained from FDA under FoI legislation. No further information expected by MSD.	0707USA00698
	27	**Anorectal disorder, demyelination, hypoaesthesia, MS, muscular weakness, nervous system disorder, MRI abnormal** Onset of numbness, muscle weakness lower L side body. Mid July loss of rectal tone. Multiple brain and spinal cord lesions.	26 Jun 07 (3)	26 Jun 07	Same day	Info obtained from FDA under FoI legislation. No further information expected by MSD.	0709USA01312
	17	**MS, Infectious mononucleosis, platelet count increased, ESR increased, headache, myelitis transverse, neuromyelitis optica** Headache, fever, muscle aches, dizziness, paraesthesia and ataxia MRI suggestive of transverse myelitis or ADEM. Subsequently developed urinary retention. MRI showed multiple brain lesions.	5 July 07 (1)	3 Sept 07	8 weeks	Concomitant admin of second dose of varicella vaccine. Also received meningococcal vaccine in July. Physician report. No further information expected by MSD.	0710USA02905

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
	18	**Syncope, malaise, optic neuritis, CNS lesion, loss of consciousness, pupils unequal, dizziness, headache** L anisocoria on day of dose 1 On day of second dose L anisocoria, headache, dizziness, syncope. Optometrist diagnosed optic neuritis MRI 21 Aug 07 showed 11 small subcortical white matter lesions. CSF exam'n Dec 07 was normal Rpt MRI Mar 08 – no new lesions	19 Mar 07 (1) 4 Jun 07 (2)	19 Mar 07 4 Jun 07	Same day Same day	Two neurologists, including an "MS specialist" did not think it was MS. Report from "healthcare worker". No further information expected by MSD	0806USA08578
France	15	**Optic neuritis** Central scotoma. MRI normal.	14 Mar 08 (1)	Unk	Unk	Minimal information available. GP report. No further information expected by MSD	0806USA00742
	Unk	**MS** Homonymous hemianopia. MRI showed hypersignals with contrast uptake. Oligoclonal bands in CSF.	Unk (2)	8 May 08	Unk	GP report. Additional information sought by MSD.	0808USA04932
	21	**MS, hemianopia, visual field defect** R hemianopia. White matter lesions on MRI.	Feb 08 (2)	Early May	3 months	Report suggestive of symptoms prior to third dose (15 May 08). Information received from health authority. Additional information sought by MSD.	0807USA01408
	16	**MS** Loss of balance and slurred speech. Ataxia, dysarthria and pyramidal syndrome on examination. MRI several hypersignals. LP results unavailable	21 Mar 08 (1)	28 Mar 08	1 week	Report from neurologist. Additional information sought by MSD.	0806USA00741
	16	**MS, hypoacusis** Fatigue, hypacusis, paraesthesia lower limbs, hazy vision. MRI multiple lesions of white matter in hemispheres, brain stem and spinal cord.	18 Mar 08 (1)	12 Apr 08	3 weeks	GP report. No further information expected by MSD	0806USA08511
	20	**Osteoporosis, MS** Report of hospitalisation with diagnosis of osteoporosis and MS	Unk	Unk	1 month	No clinical information available - report from patient's mother via a friend. No further information expected by MSD	0801USA05399
	20	**MS** Sensory and motor disturbance of R arm. MRI Multiple hypersignals with contrast uptake. Oligoclonal bands in CSF.	6 Aug 07 (1)	20 Aug 07	2 weeks	P't subsequently had second clinical episode in Oct 07. Health professional report. No further information expected by MSD	0712USA01578

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
	20	**MS** Hypoaesthesia on defaecation without incontinence. Subsequently developed saddle paraesthesia and paraesthesia of lower limbs. MRI showed hypersignals in white matter. (thought by neurologist to be old lesions) Oligoclonal bands in CSF	27 Aug 07 (1)	12 Sept 07	2 weeks	Patient subsequently developed second clinical episode. CIS developing into CDMS. Physician report. No further information expected by MSD	0710USA02244
Germany	15	**Optic neuritis** Impaired vision R eye. Optic neuritis diagnosed - began resolving in 2 weeks with IV prednisolone. MRI and path tests normal. Vision deteriorated 19 July, requiring IV methylprednisolone. SEP normal. VEP could not be analysed. Recurrence of optic neuritis	11 May 07 (2) 9 Nov 07 (3)	23 Jun 07 18 Dec 07	6 weeks 5 weeks	Further episode of optic neuritis in July 08. Report from neurologist. No further information expected by MSD	0803USA01333
	20	**MS, autoimmune thyroiditis** Headache from 14 Sept. MRI showed multiple periventricular foci with one lesion visible with contrast. Oligoclonal bands in CSF. Hashimoto's thyroiditis diagnosed Dec 07	13 Sep 07 (2)	14 Sep 07	1 day	Reports of episode of headache and paraesthesia in arms and legs 4 years prior with seven episodes in intervening period. Report from health authority. No further information expected by MSD	0808USA04762
	19	**MS** "symptoms of MS"	Jan 08 (2)	17 Jun 08	5 months	Poorly documented. No clinical or diagnostic information. GP report. Additional information sought by MSD.	0806USA09126
	24	**MS** Paraesthesia L side body excluding face. Resolved without treatment. Jan 08 experienced numbness R leg which recovered with cortisone. April 08 visual disturbance R eye. Abn SEP L median nerve April 08. Abn SEP R tibial nerve Feb 08. Oligoclonal bands in CSF. MRI 2 lesions in spinal cord, 3 lesions in brain.	16 Oct 07 (2)	19 Oct 07	3 days	CIS developing into CDMS. Report from health authority. No further information expected by MSD	0804USA00348
	18	**MS, herpes zoster** URTI in mid Feb. Followed on 20 Feb by blurred vision, reduced VA, nystagmus with decelerated VEP. Oligoclonal bands in CSF. MRI showed swelling of optic nerve and suspect lesions in periventricular medullary layer. Treated with steroids. Later developed HZ.	7 Feb 08 (3)	14 Feb 08	7 days	CIS. Report from GP. No further information expected by MSD	0804USA00349

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
	20	**MS** Symptoms consistent with Lhermitte's sign. From Jan 08 recurring paraesthesia fingers. VEPs abn both sides. Oligoclonal bands in CSF. Multiple parietofrontal demyelinations on MRI.	16 Oct 07 (?)	30 Oct 07	2 weeks	GP report. Additional information sought by MSD.	0804USA05603
	17	**Leukoencephalomyelitis, Mycoplasma infection, MS** Ophthalmoplegia, diplopia, ataxia. Oligoclonal bands in CSF. MRI showed multiple lesions in brain. Serology positive for Mycoplasma pneumoniae.	27 Mar 08 (2)	7 Apr 08	10 days	Aug 08 Paraesthesia and persistence of diplopia MRI showed new lesion. Paediatrician report. No further information available.	0804USA06200
	17	**MS, brain stem syndrome, nystagmus** Headache somnolence and dizziness, nystagmus and diplopia. MRI and CSF normal. Recovered with steroids. Recurrence of symptoms at unspecified time Disseminated lesions on MRI	28 Feb 08 (3)	10 Apr 08	6 weeks	MS diagnosed on basis of 2 episodes and disseminated lesions on MRI. Physician report. No further information expected by MSD	0805USA02846
	17	**MS, pyrexia, URTI, radial nerve palsy** Asthenia, paraesthesia R hand. Recovered. Initial diagnosis radial nerve palsy Diplopia, headache, dizziness and fever. Recurrence of paraesthesia. Oligoclonal bands in CSF. MRI multiple brain lesions.	9 Jul 07 (2) 22 Nov 07 (3)	16 Jul 07 13 Dec 07	7 days 21 days	CIS developing into CDMS. Physician report. No further information expected by MSD	0801USA03199
	20	**MS** Numbness and paraesthesia both arms and legs MS diagnosed	10 Jul 07 (2)	13 Sept 07	8 weeks	Poorly documented. Minimal information. No diagnostic test results available. Physician report. No further information expected	0711USA03299
	15	**Headache, injection site pain,CSF protein increased, MS, eyelid ptosis, incorrect route of administration** Headache of undocumented duration but recovered. Report of blood in syringe at time of vaccination MRI (Nov 07) non specific hyperintensity. Uncorroborated report of ptosis ?ADEM	4 June 07 (1)	June 07	?2 days	Minimal information. Physician report. No further information expected by MSD	0708USA00836
	18	**MS** L sided headache, paraesthesia & dysaesthesia on R side body. Oligoclonal bands in CSF. MEP, VEP, MRI normal. FDE ?ADEM	26 Jul 07 (2)	17 Aug 07	3 weeks	Initial report from gynaecologist. Patient's mother subsequently reported a diagnosis of **MS** was confirmed by neurologist. No further information expected by MSD	0709USA02570

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
Sweden	21	**MS** "Changed sensitivity" soles of feet, ascending to groin. Multiple lesions brain and spinal cord on MRI.	6 Nov 07	20 Nov 07	2 weeks	CIS. Report from "health professional". Physician report. No further information expected by MSD	0803USA03240
Canada	20	**MS** "Patient experienced multiple sclerosis". MRI said to be confirmatory.	Jan 08 (3)	May 08	5 months	Poorly documented. Minimal information. No actual diagnostic test results reported. Physician report. No further information expected by MSD	0806CAN00053
Morocco	17	**MS** "Neurological disorder" Diagnosis of MS	3 Aug 07 (1)	Oct 07	8 weeks	Poorly documented. Minimal information. No diagnostic test results available. Report from paediatrician. Additional information has been sought by MSD.	0712USA02198
Austria	25	**Leukoencephalomyeltitis, optic neuritis** Blindness L eye. Hyperintense areas on brain MRI. Oligoclonal bands in CSF	28 Mar 07 (1)	30 Apr 07	4 weeks	Patient subsequently received second and third doses without sequelae. Physician report. No further information available.	0804USA02595
	16	**MS** Blindness R eye. MRI showed chronic demyelination process.	25 Oct 07 (1)	15 Nov 07	3 weeks	Minimal information. Report from gynaecologist. Austrian health Authority said to have "confirmed diagnosis of MS"	0802USA02225
Spain	16	**Optic neuritis** Sudden loss of vision L eye, defective visual fields in both eyes.	May/June 08 (1)	24 Jun 08	3 weeks	Minimal information. No diagnostic test results available. Report from "health professional".	0807USA01420
Australia	24	**Vision blurred, optic neuritis, scotoma** Blurred vision with scotoma. Acute macular neuroretinopathy (AMN)	Unk	25 July 07	Unk	Based on ADRS case line listing	0805AUS00033 ADRS 234408
	25	**MS, hemiparesis, lethargy** Symptoms initially consistent with viral encephalitis. R sided weakness. May June 08 diagnosed with MS on MRI findings	1 Nov 07 (2)	Unk	Unk	Report from physician via CSL.	0807AUS00041 ADRS 242796
	16	**MS, tooth extraction, depression, pharyngitis, optic neuritis** R face, arm and leg numbness, then discrete episode of blurring vision in R eye. MRI – inflammatory changes R optic nerve and brain consistent with demyelination	25 July 07 (2)	Oct 07	63 days	Report from neurologist via CSL	0801AUS00163 ADRS 237812

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
	21	**MS relapse, optic neuritis, paraesthesia** Relapse characterised by transverse myelitis and optic neuritis	30 Oct 07 (2)	31 Oct 07	1 day	Report from physician via CSL	0711AUS00143 ADRS 236306
	17	**MS, paresis** Numbness descending on torso from armpits to include legs and feet over two week period. Brain and spine MRI – three spinal lesions. Also complained of flickering in R eye and visual loss	15 Apr 07 (1)	22 Apr 07	1 week	Based on ADRS case line listing	0808AUS00036 ADRS 243264

Shading denotes cases with elements suggestive of positive rechallenge, discussed in the main body of the report.

TABLE NINETEEN Gardasil - Australian reports of new onset chronic disease of possible autoimmune aetiology

Body system and disease	ADRS Nos.	Patient age	Dose	Latency	New onset disease?	ADRAC Causality Code	Comment
Connective tissue							
Rheumatoid arthritis	235066	23	2	NR	Yes	Possible	Self report. Diagnosis said to have been made by rheumatologist.
	235452	22	NR	"A few days"	No	Possible	Major flare of synovitis in wrists and MTP joints, requiring prednisone.
	237079	22	NR	"A few days"	No	Possible	Duplicate of 235452
Arthritis	228979	16	1	Same day	Yes	Possible	Swollen R foot and wrist same day. Resolved in 24hrs with topical, oral antihistamines. More likely allergic react'n than arthritis.
Polyarthritis	234501	13	NR	10 days	Yes	Possible	ANA positive. Treated with NSAIDs
Arthropathy	Nil						
Reactive arthritis	Nil						
Scleroderma	Nil						
SLE	Nil						
Wegener's granulomatosis	Nil						
Sjogren's syndrome	Nil						
Goodpasture's syndrome	Nil						
Systemic necrotising vasculitis	Nil						
Antiphospholipid syndrome	236663	20	2	26 days	Yes	Possible	P't with RA and on OCP developed DVT. High anticardiolipin IgG titre (>64) and anti-β 2 glycoprotein (137gU; N<20). Pts with autoimmune diseases may have antiphospholipid antibodies.

Dermatological							
Psoriasis	240128	17	1	NR	Yes	Certain	Guttae psoriasis Positive rechallenge with second dose
	235326	17	1	2 days	Yes	Possible	Guttae psoriasis. Saw dermatologist
	229154	17	1	16 days	Yes	Possible	Guttae psoriasis. Saw dermatologist
	230579	17	1	16 days	Yes	Possible	Duplicate of 229154
Stevens Johnson Syndrome	Nil						
Raynaud's Disease	Nil						
Alopecia	237051	26	2	18 days	Yes	Possible	Minimal information
	244417	15	2	9 weeks	Yes	Possible	Minimal information via NSW Health
Cutaneous lupus	Nil						
Dermatomyositis							
Dermatitis herpetiformis	Nil						
Erythema nodosum	Nil						
Vitiligo	Nil						
Pemphigus vulgaris	Nil						
Pemphigus foliaceus	Nil						
Endocrine							
Thyroiditis	Nil						
Hashimoto's Disease	Nil						
Grave's Disease	Nil						
Goitre	235085	14	2	1 week	Yes	Possible	Small painful goitre and cervical lymphadenopathy following viral like illness one week after vaccination. All tests clear (esp inflammatory markers and antithyroid antibodies) and cause of symptoms remain unknown.

Hypothyroidism	Nil						
Hyperthyroidism	Nil						
Lymphocytic hypophysitis	244770	19	1	4 weeks	Yes	Possible	Presented with headache and polyuria consistent with diabetes insipidus
Diabetes mellitus	230283	16	2	Same day	No	Possible	Report of hyperglycaemia, tachycardia, palpitations, lip oedema for 24hrs.
Gastrointestinal							
Coeliac disease	240684	12	1	3 weeks	Yes	Possible	Minimal information
Crohn's Disease	Nil						
Ulcerative colitis	Nil						
Ulcerative proctitis	Nil						
Inflammatory bowel disease	Nil						
Haematological							
Autoimmune haemolytic anaemia^	Nil						
Pernicious anaemia	Nil						
Autoimmune thrombocytopenic purpura*	Nil						
Other							
Uveitis	Nil						
Nephritis	Nil						
Autoimmune glomerulonephritis	Nil						
Sarcoidosis	Nil						
Addison's Disease	Nil						

Dark shading denotes cases of new onset disease and light shading denotes cases exacerbations of disease discussed in the main body of the report.
* ADRS No. 243399 was a report of ITP - antibody screen and direct antiglobulin test were negative. ^ There was a single case (ADRS No. 235058) of acute haemolytic anaemia with cold amplitude IgG. Patient recovered with high dose steroids and transfusion. Reportedly no evidence of viral, autoimmune or lymphoproliferative origin.

FIGURE ONE

Gardasil - Australian reports of pancreatitis

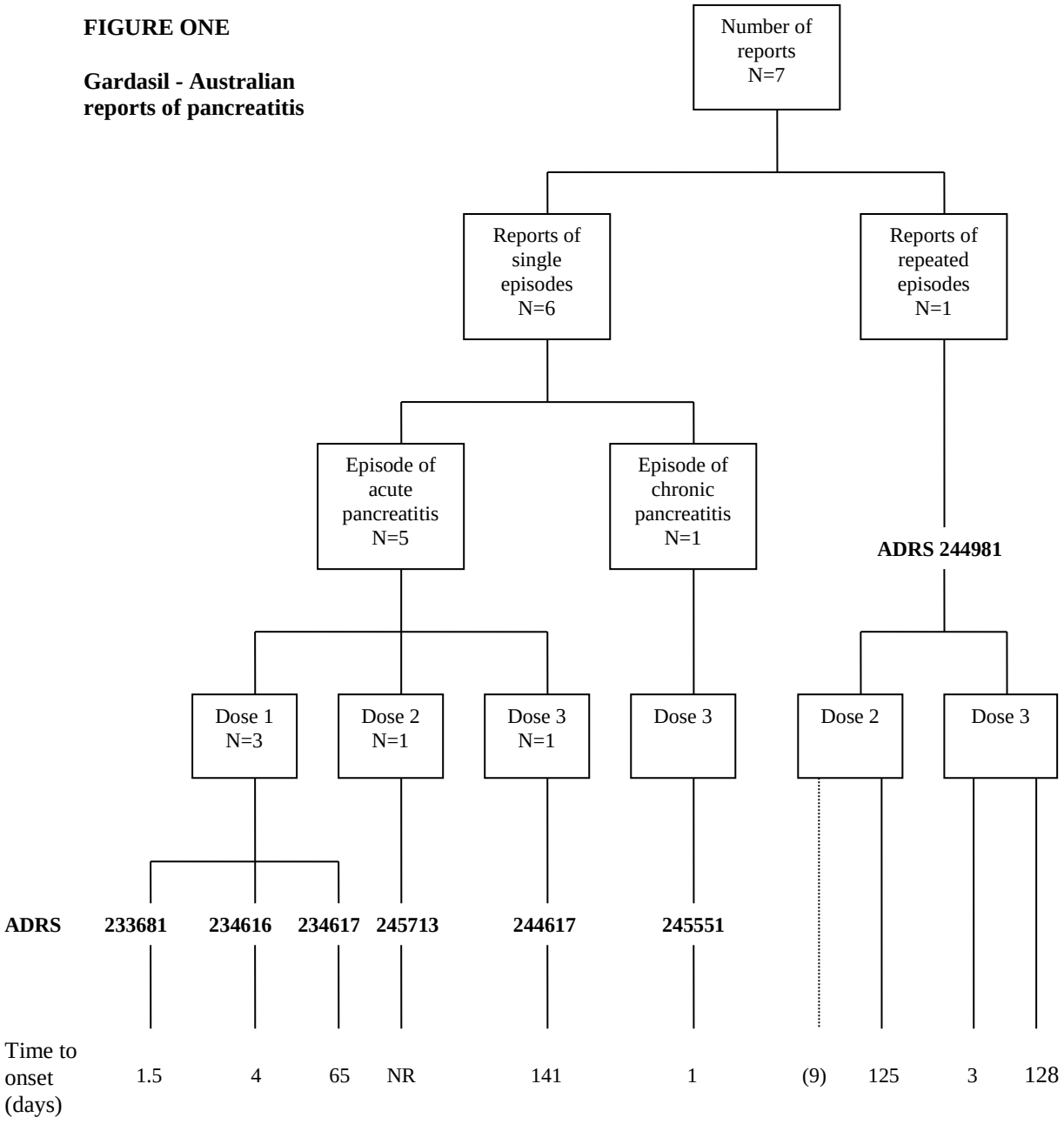

TABLE TWENTY Australian spontaneous Gardasil ADR reports of pancreatitis and hepatitis

ADRS No. (1^0 reporter)	Age/ DoB	Vacc dose	Latency	Presentation and investigation (Reaction terms bolded)	Other meds/risk factors	Comment
Pancreatitis						
233681 (GP)	19yrs 09/11/87	1	1.5 days	Sudden onset **epigastric pain** with RUQ tenderness. **Pancreatic enzymes increased** - amylase (128; RR 20-100) and lipase (109; RR 0-60) and normal LFTs. Treated with panadeine forte. Enzyme levels returned to normal after 24 hrs (amylase 46, lipase 41).	Long standing use of OCP (Levlen). Upper abdominal U/S normal. Does not drink alcohol. Note: Viral screen not performed, not investigated further.	Mild pancreatitis. No further episodes. Note: did not have second or third dose.
234616 (Hospital RMO)	26yrs 02/09/81	1	4 days	Severe constant **epigastric pain** and vomiting with marked epigastric tenderness, preceded by **rash** and **fever** (40^oC). **Amylase increased** (1900U/L; RR: 23-85) and **lipase increased** (3400U/L; RR: 0-160). Serum calcium was normal. CT Scan showed grossly oedematous pancreas and ascites. Diagnosis of **pancreatitis** Reported in MJA 2008; 189(3): 178.	No history of gallstones. No alcohol consumption. Normal metabolic screen Serology negative for coxsackie A9, B1-6; echo, mumps, herpes simplex, hepatitis and varicella zoster viruses. MRCP showed no pancreatic parenchymal or ductal abnormality. Patient given Phenergan and doxycycline for rash occurring on day 2 post vaccination.	Pancreatitis with no identifiable cause. Confounded by use of Phenergan and doxycycline 2 days prior to abdominal symptoms. Authors postulated an autoimmune causality.
234617 (GP)	24yrs	1	65 days	R sided abdominal pain and nausea. Elevated serum lipase (711; RR 13-60 U/L) and free fluid in peritoneal cavity on ultrasound. Diagnosis of acute **pancreatitis**.	No history of or U/S evidence of gallstones. Metabolic screen normal except for mildly elevated serum Ca on admission (later N). No history of excessive alcohol intake. MRCP normal. Viral screen not performed. Longstanding OCP (Microgynon 20). Low B12 levels but tests for pernicious anaemia (IF and parietal cell Abs) negative. RF positive 16 (RR <14) – done during investigation of Raynaud's-like symptoms.	Acute pancreatitis unknown cause. No further episodes. Note: did not have second or third dose. Reporter questioned propensity toward autoimmune disorders.

TABLE TWENTY c't'd Australian spontaneous Gardasil ADR reports of pancreatitis and hepatitis

ADRS No. (1^0 reporter)	Age/ DoB	Vacc dose	Latency	Presentation and investigation (Reaction terms bolded)	Other meds/risk factors	Comment
Pancreatitis						
244617 (GP)	20yrs 6/1/88	3	141 days	Report of **pancreatitis** with lipase of 2025 (units and RR not reported). Presented with 4 hour history of abdominal pain. Hospitalised (St Vs Sydney) overnight and treated with IV fluids.	Use of OCP (Levlen). Alcohol consumption <6 standard drinks per month. Results of U/S done in St Vs Sydney not available. Patient has not represented for further investigation (Rpt U/S ordered) Not clear if viral or metabolic screen done at time of episode.	Report via MSD from GP, based on hospital discharge summary. Report prompted by MJA article.
244981 (Patient)	25yrs 25/12/81	2	9 days	Oct 07 - **Abdominal pain** and **chest pain**. GP diagnosed viral gastroenteritis.	Use of OCP (Marvelon) from Jan 08 Limited viral screen in May – Hep C negative, Hep BsAg negative, Hep A Ab positive. Serum calcium and lipids (Sept 08) normal. MRCP showed no pancreatic parenchymal or ductal abnormality and intrahepatic and extrahepatic biliary tree normal.	First episode of pain not diagnosed as pancreatitis. However, characteristics similar to symptoms experienced when she was subsequently diagnosed as suffering from pancreatitis. ? Positive rechallenge.
		2	125 days	Feb 08 - Severe **abdominal pain** and **chest pain**. Not hospitalised. Reported diagnosis of **pancreatitis**.		
		3	3 days	April 08 - Severe **abdominal pain** and **chest pain**. Found to have elevated serum amylase (792 U/L; RR 10 – 100). US – no gallstones. Saw GE– diagnosis of biliary colic with pancreatitis. CT cholangiogram (May 08) showed normal biliary system with ?layering in gallbladder consistent with very small calculi.		
		3	128 days	Aug 08 – Severe **abdominal pain**, nausea and dry retching. Preceded by 1 week of sore throat and flu-like symptoms and antibiotic treatment. Admitted Maroondah Hospital. Elevated lipase. MRCP in Oct 08 (organised by another GE) was completely normal. At last follow up GE stated diagnosis has not been elucidated.		

TABLE TWENTY c't'd Australian spontaneous Gardasil ADR reports of pancreatitis and hepatitis

ADRS No. (1^0 reporter)	Age/ DoB	Vacc dose	Latency	Presentation and investigation (Reaction terms bolded)	Other meds/risk factors	Comment
Pancreatitis						
245551 (Physician)	13yrs 17/7/94	3	1 day	Persistent epigastric pain without vomiting, anorexia or fevers worsening after 2 weeks at which time serum lipase was found to be elevated (1272U/L) and later peaked at 5920. LFTs and abdominal US were normal. Hospitalised for 10 days and treated with NBM and NJ feeding. Discharged on oral fluids and NJ feeds. Readmitted to hospital 3 weeks later with 3 to 4 days of worsening abdominal pain and elevated lipase (7944). Diagnosis of acute on **chronic pancreatitis**	"All investigations for cause of her pancreatitis have been normal".	
245713 (Patient)	19yrs 29/4/89	2	NR "after.. inject^{n}"	Fever and sweating followed a week later by back and abdominal pain. Hospitalised for 4 days with final diagnosis of **pancreatitis** – no cause found.	Alcohol intake normal. No organic cause on CT imaging.	Anonymous report via AME Line. No additional information available
Hepatitis						
244616 (GP)	14yrs	2	1 day	Severe **hepatitis** requiring hospitalisation. No cause was found. Settled over 2 weeks. LFTs: AST 443 U/L (NR <45); ALT 741 U/L (NR <45), γGT 72 U/L (NR 0-30). Amylase 43 U/L (NR 36-128). Serology for hep A &B, EBV, CMV, adeno and enterovirus negative	Had cholecystectomy 2002 at age 8. Abdominal ultrasound performed during hospital admission excluded intrahepatic cholestasis.	

TABLE TWENTY ONE Summary of global reports to MSD with reaction terms pancreatitis/acute pancreatitis/pancreatic enzymes increased

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
USA	18	**Pancreatitis** Sudden attack of pancreatitis with severe abdominal pain. Hospitalised and recovered over 3 to 4 weeks. After second dose experienced another episode of pancreatitis. Not hospitalised but sought medical attention. Recovered over 3 to 4 weeks Another episode of pancreatitis	14 Mar 07 (1) 16 May 07 (2) 20 Sept 07 (3)	15 Mar 07 May 07 Sept 07	24 hours Unk Unk	Report from a "medical assistant". No results of serum amylase, lipase or CT/MRI reported. Likely positive rechallenge x 2.	0710USA00203
	13	**Pancreatitis, loss of consciousness, asthenia, nausea, pyrexia, paralysis, pain, chest pain, abdominal pain** Fever and pain on day of injection. Following day developed chest and abdominal pain and vomiting. Was hospitalised with pancreatitis, requiring two surgeries. Also reported by a physician that patient's lower arms and legs were "paralysed as a result" Apparently also had a syncopal episode after a dose reported to have been administered on 1 Apr 08 (note inconsistent dates).	27 Feb 07 (2)	27 Feb 07	Same day	Report of pancreatitis was via a lawyer. No confirmatory diagnostic information available. Concomitant vaccination with diphtheria toxoid, pertussis acellular vaccine and tetanus toxoid MSD has requested further information.	0804USA01963
	13	**Pancreatitis** Report of patient developing pancreatitis that required hospitalisation and significant medical intervention	Unk	Unk	4 weeks	Report from a nurse via a physician, based on a radio report. Minimal information MSD has requested further information	0807USA03601
	Unk	**Pancreatitis** Patient discharged from hospital in August 2008 after 8 weeks treatment for an episode of pancreatitis. First dose of Gardasil was said to have been administered some time in 2006.	Unk (3) ?06 ?07	Unk 08	Unk	Report from nurse with minimal information. No further information expected by MSD	0808USA03111

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
	16	**Pancreatitis acute, iron deficiency anaemia, abdominal pain, dyslipidaemia, hypertriglyceridaemia, inflammation, malnutrition, obesity, pyrexia** Hospitalised for 5 days with pancreatitis. One day history of abdominal pain, fever. Serum amylase 112. Found to have leucocytosis WCC 21.1 x 10^9, serum cholesterol 223, HDL-C 62, LDL-C 109, serum triglycerides 260, ESR 55. Noted to be obese and found to have protein malnutrition and iron deficiency anaemia. CT scan showed peripancreatic stranding consistent with pancreatitis.	23 May 08 (3)	2 Jul 08	40 days	Diagnosis of acute pancreatitis possibly secondary to hypertriglyceridaemia. On OCP (ethynyl oestradiol + norelgestromin) Patient's sister also had pancreatitis at about the same age and has been recently diagnosed with diabetes mellitus.	0808USA04473
	10	**Abdominal discomfort, arthralgia, immediate post injection reaction, influenza like illness, musculoskeletal pain, pancreatitis, stomach discomfort** Upset stomach immediately after second injection. On 18 Apr 08 experienced flu-like symptoms Hospitalised on 27 Apr 08 with pancreatitis for 4 days, followed by residual abdo pain. No explanation for her pain – has had blood tests, CT scan, endoscopy, colonoscopy. Aug 08 experienced shoulder joint pain	25 Jan 08 (1)	27 Apr 08	3 months	No actual investigation results provided. Info obtained from FDA under FoI legislation. No further information expected by MSD.	0809USA02793
Australia	26	**Rash generalised, abdominal pain upper, blood amylase increased, lipase increased, pancreatitis, pyrexia** Severe constant epigastric pain and vomiting with marked epigastric tenderness. Amylase increased (1900U/L; RR: 23-85) and lipase increased (3400U/L; RR: 0-160). Serum calcium normal. CT grossly oedematous pancreas, ascites	27 Sept 07 (1)	29 Sept 07	2 days	Report by Das et al in MJA 2008 Received Phenergan and doxycycline for rash and fever prior to onset of pancreatitis	0805AUS00050 ADRS 234616
	24	**Pancreatitis** Patient developed pancreatitis and was hospitalised. Serum calcium 2.63 mmol/L (NR 2.10-2.60) and lipase 711 U/L (NR 13-60).	15 July 07 (?)	18 Sept 07	65 days	Information based on original ADRS line listing. Additional information was sought by TGA from the patient's GP – see Table Ten	0805AUS00064 ADRS 234617
	20	**Pancreatitis, inappropriate drug administration** Patient experienced acute pancreatitis and was hospitalised. Lipase 2025 (units not specified). No cause for pancreatitis was identified.	25 Feb 08 (3)	4 Aug 08	141 days	Concomitant use of OCP (Levlen)	0808AUS00325 ADRS 244617

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
Germany	15	**Acute pancreatitis** "Patient experienced acute pancreatitis".	7 Feb 08 (3)	6 Mar 08	4 weeks	Minimal information via physician report. No results of serum amylase, lipase or CT/MRI reported. Concurrent meds levothyroxine sodium and potassium iodide	0803USA02574

TABLE TWENTY TWO Summary of global reports to MSD with reaction term hepatitis

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
USA	Unk	**Hepatitis, abdominal pain** Patient experienced a recurrence of hepatitis and abdominal pain	Unk	Unk	Unk	Almost no information provided in report. Physician report. MSD has requested further information.	0610USA05710
	12	**Hepatitis** At visit for second dose, the patient's mother advised that patient had been diagnosed with autoimmune hepatitis	Unk (1)	Unk	"<2 months"	Minimal information. Physician report. MSD has requested further information.	0701USA00228
France	16	**Hepatitis** LFTs – SGOT 145, SGPT 57 (NR not reported). Hep A, B and C serology negative.	25 Feb 08 (?)	15 Mar 08	19 days	Report from local health authoritiy. Minimal information with no further information expected by MSD. Incomplete diagnostic workup. Patient received further dose on 14 April 08 without incident	0809USA02948
	18	**Hepatitis, incorrect route of drug administration** Third dose given subcutaneously instead of intramuscularly. Developed hepatitis with γGT 33 and transaminases 52.9. Serology for hepatitis B and C were negative. CMV serology apparently done but results not reported. No history of excessive alcohol intake	20 Feb 08 (3)	April 08	6 weeks	Report from GP. Minimal information with no symptomatology reported and incomplete diagnostic workup.	0808USA04578
	14	**Hepatitis, vulvitis** Developed oedematous vulvitis 11 days post injection, which lasted for 7 days. On 24 May 08 blood tests were performed (reason not given) and showed elevated SGOT 138 and SGPT 34 (NRs not reported)	7 Apr 08 (1)	18 Apr 08	11 days	Report from GP. Minimal information with no symptomatology reported and incomplete diagnostic workup. Reason for LFTs not stated	0806USA03640
Germany	17	**Lyme disease, skin necrosis, hepatitis, rash** Patient experienced borreliosis followed by a neurodermatitis-like rash with skin necrosis and hepatitis. Patient presented to two naturopaths where kinesiologic testing was said to have revealed a severe disturbance of the whole body, especially liver and spleen.	28 Dec 06 (1)	Mar 07	3 months	Report from patient's mother via gynaecologist. No actual investigation results provided.	0711USA03027

Country	Age	Reaction term(s) recorded on the CIOMS form Clinical manifestation, investigation & diagnoses	Vacc date (dose)	Reaction onset	Latency	Comment	WAES Number
	14	**Anaemia haemolytic autoimmune, hepatitis, Cushingoid** Hospitalised with jaundice and abnormal LFTs. Serology for hepatitis A & B viruses, EBV, CMV and toxoplasmosis were all negative. Readmitted 25 Feb 08 with severe pallor. Hb 4.9g/dL. Direct Coombs test positive and abdo US showed hepatosplenomegaly. Anti-erythrocytic warm autoantibodies found. Treated with immunosuppressive therapy including prednisone and patient became Cushingoid.	3 Jan 08 (2)	8 Feb 08	36 days		0804USA02722
	18	**Rhabdomyolysis, hepatitis, polyneuropathy, sports injury** Sports injury (bruise to head) 8 Nov 07. Developed muscle pain in all limbs on 13 Nov 07, which eased leaving only pain in lower legs. Hospitalised 21 Nov 07 with suspected rhabdomyolysis. CK elevated 1874U/L (NR 10 – 145) and LDH 327U/L (NR < 248). Liver function tests also abnormal with elevated SGPT 615U/L (NR <34); SGOT 200U/L (NR <31) and γGT 258U/L (NR <38). Lymphopenia and monocytosis also noted. Serology for EBV, CMV, Borrelia, influenza and Coxsackie B virus were negative. Patient recovered over a few days. Patient was hospitalised on 10 Dec 07 because of neuropathic pain in lower limbs. Repeat tests were normal apart from a slightly elevated γGT 47U/L. EMG was normal. NCS showed slightly reduced velocities in lower legs. Final diagnosis polyneuropathy most probably of para-infectious aetiology.	6 Sep 07 (2)	13 Nov 07	2 months	Patient had third dose of Gardasil in Feb 08 without incident	0803USA03411

Shading in this table indicates noteworthy cases, identified in the main body of this report

TABLE TWENTY THREE Australian spontaneous Gardasil ADR reports of vulvovaginal lesions

ADRS No.	Age	Vacc dose	Latency (days)	**Reaction terms/**clinical features and investigations	Comment	Primary reporter
228983	12	1	0	**Vaginal itching, pruritic rash, rash maculovesicular** 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. Past history of eczema.	Vaginal itching probably part of a generalised allergic-type reaction	Mother via health dep't
230355	20	NA	1	**Vulvovaginal candidiasis** Nil recent antibiotics		GP
233544	20	NA	2	**Vaginal bleeding** Breakthrough menstrual bleeding with light spotting lasting 4 weeks. Last period 1 week prior to Gardasil was normal and cycle was previously regular. All investigations normal. Treated with OCP.		GP
233734	17	NA	NA	**Thrush vaginal, fever, malaise** Report of recurrent episodes of vulvovaginal candidiasis commencing "after" first dose. Experienced 4 episodes with last reported episode occurring within 24 hours of a gardasil injection. On that occasion also felt unwell and was febrile for 24 hours.		GP
234004	16	2	0	**Vaginal swelling, vaginal haematoma, vaginal mucosal blistering, fever, influenza-like symptoms, myalgia, tiredness, vaginal ulceration** Patient developed vaginal swelling, discoloration and blistering, and a fever (40°C) in the evening after immunisation the evening after vaccination. Presented to emergency department and was referred to gynaecology clinic, where investigation included biopsy and serology. Biopsy showed non specific inflammation. Other diagnostic tests were viral swab, full STD screen, blood culture, FBC and urinalysis which revealed negative results. Not sexually active.	Specialist gynaecologist noted the girl had been riding an exercise bike in the days preceding vaccination and considered the swelling, blistering and subsequent ulceration to be due to inflammation (secondary to trauma).	Dr via health dep't

TABLE TWENTY THREE c't'd Australian spontaneous Gardasil ADR reports of vulvovaginal lesions

ADRS No.	**Age**	**Vacc dose**	**Latency (days)**	**Reaction terms/**clinical features and investigations	**Comment**	**Primary reporter**
234508	17	NA	14	**Genital ulceration** 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.	It was noted the patient had undergone testing for herpes simplex prior to receiving Gardasil, for reasons not stated.	GP
234884	16	1	3	**Vaginal ulceration, fever, backache, rigors** Perivaginal and vulval ulceration and labial swelling a few days after immunisation and required hospitalisation. Treated empirically with IV acyclovir. Patient reportedly not sexually active. Testing negative for HSV I & II, varicella zoster, CMV and STDs. Vaginal swab M/C/S clear. FBC and LFT normal. Urine electrolyte test normal.		GP
235391	16	1	2	**Vaginal ulceration** Developed vaginal inflammation and blistering 2 days after immunisation; the lesions resolved 7 days later.	Also received Fluvax and Vivaxim (Hep A + Typhoid) vaccinations. Patient did not seek medical attention during the event	Other health professional
235450	25	NA	1	**Vulval irritation** Vulva became erythematous and inflamed, which worsened over next 6 days. Treated with topical steroids.	Very limited information available	Health dep't
235631	17	1	1	**Pruritus, vesicular rash, vaginal irritation** 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 patient was referred to a dermatologist.	Vaginal irritation probably part of a generalised allergic-type reaction	Parent
236132	23	NA	0	**Vulvovaginal papilloma** Developed new vulvovaginal warts after immunisation.	Likely flare-up of an existing HPV infection. The vaccine does not contain a live virus so there is no risk of cross-infectivity	GP

TABLE TWENTY THREE c't'd Australian spontaneous Gardasil ADR reports of vulvovaginal lesions

ADRS No.	**Age**	**Vacc dose**	**Latency (days)**	**Reaction terms/**clinical features and investigations	**Comment**	**Primary reporter**
238693	24	1	NA	**Anogenital warts, vulval disorder** "Soon after" first dose of Gardasil patient noticed a single vulval wart. After second dose she developed many more warts over her vulva and pubic area.	Likely flare-up of an existing HPV infection. The vaccine does not contain a live virus so there is no risk of cross-infectivity	GP
244781	22	1,2,3	NA	**Nausea, vomiting, headache, vaginal bleeding** Episodes of nausea, vomiting and headache and PV bleeding after each of three doses of Gardasil. After first dose the patient had bleeding that she did not feel coincided with her periods, which until then had been regular. Had spotting after second dose. Had "awful" period after third dose		Patient

TABLE TWENTY FOUR Gardasil - Duplicate reports of convulsion/seizure

ADRS No	Pt ID/ location	DOB/ age	Reporter & location	Date of Gardasil admin	Date of reaction	Reaction description
229409	NA	NA	Anon via radio Melb	Early May 07	NA	A student in the same year as her daughter (aged 17) had a seizure and fainting
229411	A	18 yrs	K (mother) via radio Melb	27.4.07	6.5.07	Seizure and fracture of two vertebrae. Child was diagnosed with juvenile epilepsy
230318	AW	22.1.89	GP Warragul Vic	27.4.07	6.5.07	Generalised seizure causing fractured T5-6. Never known to be epileptic
230606*	AW (mother KW) Warragul Vic	26.1.89	Infection Control Consultant West Gippsland Hospital Warragul Vic	4.5.07	6.5.07	Vaccinated with Gardasil on Friday. Parents found patient on Sunday morning incontinent and hysterical, appearing to have a seizure. Was sent to hospital where it was believed a grand mal seizure occurred resulting in a fracture to L6 – transferred to Austin Hospital for management.
	AW	18 yrs	MSD	4.5.07	6.5.07	18 year old female with… absence type episodes, lasting for less than 20 secs, for possibly the past three years. Patient who was sleep-deprived from a night out with friends was found in room by mother. She was calling out in pain and had been incontinent on the floor…sustained a T5/T6 fracture. Whilst in hospital an EEG showed several absence seizures. Subsequently 8 days later the patient experienced a generalised tonic clonic seizure lasting for 5 minutes. The diagnosis was juvenile absence epilepsy.

* two sources of supporting documents

FIGURE TWO Australian spontaneous Gardasil ADR reports of convulsion/seizure

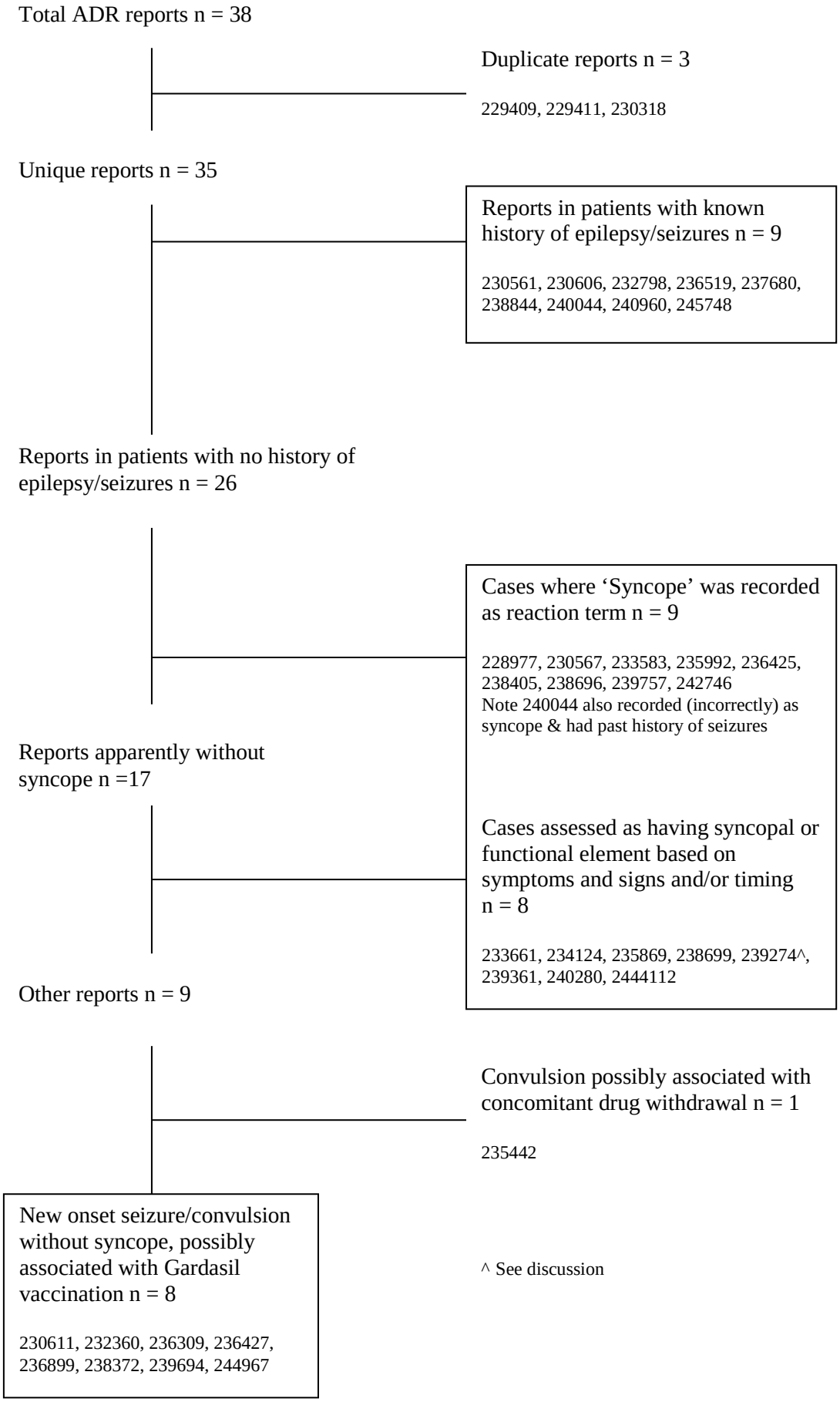

TABLE TWENTY FIVE Australian spontaneous Gardasil ADR reports of convulsions/seizures

Reports where patient had known history of convulsion/epilepsy/seizures

No.	Age	Dose	**Reaction terms**/clinical features and investigations	Latency	Comment
230561	17	1	**Convulsion, loss of consciousness** Twitching, loss of consciousness approx 1 min. Known epileptic. Medication compliance unknown.	5 min	
230606	18	1	**Epilepsy Lumber vertebrae fracture** Patient who was sleep-deprived from a night out with friends was found in room by mother. She was calling out in pain and had been incontinent on the floor. Hospitalised and found to have sustained a T5/T6 fracture. History of absence type episodes, lasting for less than 20 secs, for possibly the past three years. Whilst in hospital an EEG showed several absence seizures. Subsequently 8 days later the patient experienced a generalised tonic clonic seizure lasting for 5 minutes. The final diagnosis was juvenile absence epilepsy.	2 days	
232798	na	1,2	**Grand mal convulsion** Following both the first and second doses of Gardasil the patient experienced a Grand Mal seizure	na	
236519	27	2	**Grand mal convulsion, loss of consciousness** Tonic clonic jerk and loss of consciousness following 2nd Gardasil vaccine. Has had tonic, clonic jerking episodes before not related to vaccination.	na	
237680	14	2	**Convulsion, diarrhoea, malaise, vomiting** Patient experienced diarrhoea, feeling unwell, vomiting, and developed exacerbation of seizures. Known history of epilepsy but not on any medication. Also had a "reaction" after the first dose but event not described	na	
238844	14	1	**Convulsion, dizziness, pallor, somnolence, urinary incontinence** Became dizzy within minutes of vaccination and laid down. Student then commenced to have a seizure during which she was incontinent of urine. Following seizure was drowsy and pale. History of seizures since 6 years of age. No information regarding current medications	Minutes	
240044	12	2	**Convulsion, headache, injection site pain, palpitations, syncope, tremor, visual impairment, vomiting** ?? Convulsion post injection. Well post initially. Next day numbness, shaking. 6/7 later, arm hurting. Friday ?loss of consciousness, palpitations, associated headache, fever, vomiting and visual changes. Also history of febrile convulsions (mostly generalised clonic convulsions) as child. Has ongoing episodes of shaking.	6 days	Occurrence of LOC and convulsion questionable. Seen by paediatrician who diagnosed **migraine** on basis of headache, vomiting, visual disturbance and positive family history

240960	24	1	**Convulsion, loss of consciousness** LOC immediately after injection then had generalised seizure lasting 20 secs. History of epilepsy - last seizure 12 years ago and not currently medicated.	Immediate	Timing and duration of event more suggestive of syncopal origin
245748	13	3	**Convulsion, loss of consciousness, somnolence** Morning after vaccination, student had a seizure at home that lasted 10 to 15 seconds. LOC and stiffness noted by parent. History of seizures as a child – nil for 15 to 18 months. Also recent history of viral infection in the week prior to vaccination	1 day	Also received hepatitis B vaccination

Reports with reaction term "syncope"*

No.	Age	Dose	**Reaction terms**/clinical features and investigations	Latency	Comment
228977	16	1	**Convulsion, dizziness, pallor, syncope, urinary incontinence** Patient became dizzy, lost all colour, fainted and had a seizure (gave three jerks and went stiff with eyes rolled back) with urinary incontinence. Seizure lasted 10 seconds with rapid recovery	15 min	
230567	15	1	**Syncope, tonic clonic movements** Fainted post vaccine. Clonic tonic seizure noted during vasovagal episode. Recovered quickly. Faint witnessed by nurses.	~5 min	
233583	19	1	**Convulsion, syncope** Patient passed out and collapsed after vaccination, was quite rigid and displaying jerking (clonic) movements of the limb and upper body, experienced an altered state of consciousness. Past history of vasovagal episodes when having blood taken. When first observed by nurse the patient was being held up in sitting position by her mother	5 min	
235992	27	3	**Convulsion, syncope** No problems first 2 doses, fainted about 12 hours after 3rd dose and again 3 weeks later, possible seizure: clenched jaw, rigid for 20 seconds.	12 hrs, 3 weeks	Found to have low blood pressure.
236425	na	2	**Convulsion, disorientation, syncope** Patient fainted, had a seizure and immediately following that was disorientated for 2-3 minutes and had to lie down for 2 hours	na	
238405	17	na	**Convulsion, eye rolling, lethargy, malaise, pallor, syncope** Patient fainted after vaccination, went stiff, eyes rolled back and fitted. Was very pale, next day lethargic and off colour	na	
238696	15	1	**Convulsion, syncope** Immunisation team called to post vaccine area where patient was feeling faint. Upon trying to lie on floor she went stiff and had a minor fit of about 5 to 10 seconds duration. Came to immediately with no further concerns.	na	
239757	15	1	**Anxiety, convulsion, syncope** Post immunisation, patient was observed to faint, slide from her chair aided and proceeded to commence fitting. Also experiencing extreme anxiety	na	Possible functional component
242746	13	2	**Pallor, partial seizures, syncope** Following Gardasil vaccination she began to fall to the floor. After being supported to the floor, she was laid on her side and was then noted to have a 'focal fit' from which she recovered but then appeared pale but fully responsive.	Immediate	

* Note: ADRS No. 240044 also had syncope recorded as reaction term but is included under patients with known epilepsy

Reports adjudicated as having a syncopal or functional element on review

No.	Age	Dose	**Reaction terms**/clinical features and investigations	Latency	Comment
233661	22	na	**Cold sweat, convulsion** Seizure within 5 mins of Gardasil vaccine, seizure lasted <1 min, cold and clammy	5 mins	
234124	25	na	**Convulsion, loss of consciousness** After vaccination complained of soreness at injection site, Subsequently experienced loss of consciousness for 5 secs, followed by fitting for another 5 secs	na	
235869	21	na	**Convulsion, dizziness, nausea** Self report "I felt extremely nauseous (sic) and dizzy about five minutes after receiving the injection. I then collapsed and was reported to be having a seizure. Shortly after I got up I had another one. I went to hospital but no further action was taken"	5 min	
238699	23	2	**Convulsion, dizziness, eating disorder, nausea** Parental report about child who experienced a "minor" convulsion, where her eyes rolled back in her head and her whole body was shaking. Patient advised that all she could see was black. Had felt nauseated with headache and dizziness for a week after dose 1	na	Attending doctor had advised that the patient fainted. Reporter didn't agree
239274	12	1	**Status epilepticus** 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."	5 Min	ADRAC noted the patient remained neurologically normal throughout. Characteristics and time frame were inconsistent with true epileptic-type convulsions and more likely to be "functional seizures with anxiety"
239361	26	2	**Disorientation, grand mal convulsion** Patient immediately experienced tonic clonic seizures lasting for about 10 seconds and was disoriented for a further 10 seconds.	Immediate	
240280	20	na	**Grand mal convulsion** The patient was noted to be very nervous about the vaccination and requested that she be vaccinated whilst lying down. Patient experienced a tonic-clonic seizure immediately after injection	Immediate	? Functional seizures and anxiety
244112	21	2	**Tonic convulsion** Tonic clonic seizure after injection.	1 min	Had syncope with first injection after typical presyncope symptoms

Other reports

No.	Age	Dose	**Reaction terms**/clinical features and investigations	Latency	Comment
232630	13	1	**Convulsion** Since starting Gardasil course has had 4 seizure-like episodes where eyes remain open and loses ability to move limbs voluntarily but is conscious. One episode witnessed by nurse	na	Neurological assessment ongoing. Patient taking Valpro 200mg
236427	17	3	**Convulsion** Developed seizures following completion of vaccination. Total of 6 seizures in 3 months. Had EEG but results not known to reporter (a pharmacist)	1 week	
236899	27	2	**Convulsion** Developed seizures within a few hours of vaccination and was hospitalised. EEG showed temporal lobe focus	Hours	Minimal information available
236309	15	3	**Confusional state, convulsion, headache, malaise** Report of fitting, headache and feeling unwell two weeks after vaccination. Attended ED and CT scan performed but result not reported.	2 weeks	
230611	na	na	**Epilepsy** "Experienced epileptic fits which needed two nurses to control".	na	Scant information. Patient seeing specialist
235442	20	na	**Diarrhoea, Drug withdrawal convulsions, malaise, vomiting** Patient on Lexapro (escitalopram oxalate, an SSRI) – had run out of medications 6 days earlier, recent Gardasil immunisation	na	Abrupt withdrawal of SSRI may be associated with nausea, vomiting, diarrhoea, tremor, convulsions
238372	21	1	**Convulsion, loss of consciousness, somnolence** Loss of consciousness and "minor fit". Post ictal drowsiness for half an hour.	na	Minimal information
239644	18	2	**Convulsion, loss of consciousness, muscle twitching, tonic convulsion, visual acuity reduced transiently** Patient couldn't see clearly except bright lights, collapsed with observed twitching attacks and loss of consciousness for approximately 5 minutes, clenched fists and went rigid "tonic seizures".	Hours	Exact timing not available but events occurred in car on day of vaccination, so within a matter of hours at most. ? aural symptoms
244967	13	1,2	**Convulsion** Patient found "shaking" in classroom but was able to be escorted to sick bay. No LOC but noted by nurse to have altered mental state (vague). Reported to have developed "epilepsy" in March 08 after the first dose of Gardasil in Feb 08 (but not reported to TGA at that time).	? 4 weeks	Episode of shaking after second dose occurred 1 hour after injection

TABLE TWENTY SIX Estimates used in Scenario A

Percentage of doses used as 1st dose	60.0%
Percentage of doses used as 2nd dose	40.0%
Percentage of doses used as 3rd dose	0.0%
Estimated no. of females who received at least one dose	208541
Estimated no. of females who received at least two doses	139027
Estimated no. of females who received at least three doses	0

TABLE TWENTY SEVEN Scenario A results

Number of doses received	Coverage	Observation period (wks)	Expected Number (estimate)	95% lower CL of estimate	95% upper CL of estimate	90% upper CL of estimate	99% upper CL of estimate
≥1	100%	6	1.8	0.8	3.4	3.1	4.0
	100%	26	7.7	3.5	14.6	13.5	17.1
	100%	52	15.4	7.1	29.3	26.9	34.3
	80%	6	1.4	0.7	2.7	2.5	3.2
	80%	**26**	**6.2**	**2.8**	**11.7**	**10.8**	**13.7**
	80%	52	12.3	5.6	23.4	21.5	27.4
	60%	6	1.1	0.5	2.0	1.9	2.4
	60%	26	4.6	2.1	8.8	8.1	10.3
	60%	52	9.3	4.2	17.6	16.2	20.6
≥2	100%	6	1.2	0.5	2.3	2.1	2.6
	100%	26	5.1	2.4	9.8	9.0	11.4
	100%	52	10.3	4.7	19.5	18.0	22.9
	80%	6	0.9	0.4	1.8	1.7	2.1
	80%	**26**	**4.1**	**1.9**	**7.8**	**7.2**	**9.1**
	80%	52	8.2	3.8	15.6	14.4	18.3
	60%	6	0.7	0.3	1.4	1.2	1.6
	60%	26	3.1	1.4	5.9	5.4	6.9
	60%	52	6.2	2.8	11.7	10.8	13.7

TABLE TWENTY EIGHT Estimates used in Scenario B

Percentage of doses used as 1st dose	50.0%
Percentage of doses used as 2nd dose	37.5%
Percentage of doses used as 3rd dose	12.5%
Estimated no. of females who received at least one dose	173784
Estimated no. of females who received at least two doses	130338
Estimated no. of females who received at least three doses	43446

TABLE TWENTY NINE Scenario B results

Number of doses received	Coverage	Observation period (wks)	Expected Number (estimate)	95% lower CL of estimate	95% upper CL of estimate	90% upper CL of estimate	99% upper CL of estimate
≥1	100%	6	1.5	0.7	2.8	2.6	3.3
	100%	26	6.4	2.9	12.2	11.2	14.3
	100%	52	12.9	5.9	24.4	22.4	28.6
	80%	6	1.2	0.5	2.3	2.1	2.6
	80%	**26**	**5.1**	**2.4**	**9.8**	**9.0**	**11.4**
	80%	52	10.3	4.7	19.5	18.0	22.9
	60%	6	0.9	0.4	1.7	1.6	2.0
	60%	26	3.9	1.8	7.3	6.7	8.6
	60%	52	7.7	3.5	14.6	13.5	17.1
≥2	100%	6	1.1	0.5	2.1	1.9	2.5
	100%	26	4.8	2.2	9.2	8.4	10.7
	100%	52	9.6	4.4	18.3	16.8	21.4
	80%	6	0.9	0.4	1.7	1.6	2.0
	80%	**26**	**3.9**	**1.8**	**7.3**	**6.7**	**8.6**
	80%	52	7.7	3.5	14.6	13.5	17.1
	60%	6	0.7	0.3	1.3	1.2	1.5
	60%	26	2.9	1.3	5.5	5.0	6.4
	60%	52	5.8	2.6	11.0	10.1	12.9

TABLE THIRTY Estimates used in Scenario C

Estimated no. of females who received at least one dose	95006
Estimated no. of females who received at least two doses	91289
Estimated no. of females who received at least three doses	83845
Female enrolled population	114000

TABLE THIRTY ONE Scenario C results

Number of doses received	Coverage	Observation period (wks)	Expected Number (estimate)	95% lower CL of estimate	95% upper CL of estimate	90% upper CL of estimate	99% upper CL of estimate
≥1	100%	6	0.1	0.0	0.3	0.3	0.4
	100%	**26**	**0.4**	**0.1**	**1.2**	**1.1**	**1.5**
	100%	52	0.8	0.2	2.5	2.2	3.1
≥2	100%	6	0.1	0.0	0.3	0.2	0.3
	100%	26	0.4	0.1	1.2	1.0	1.5
	100%	52	0.8	0.2	2.4	2.1	3.0
Enrolled population	100%	6	0.1	0.0	0.3	0.3	0.4
	100%	**26**	**0.5**	**0.1**	**1.5**	**1.3**	**1.8**
	100%	52	1.0	0.2	2.9	2.6	3.7

FIGURE THREE **Authority prescriptions for MS immunomodulatory agents in female patients < 31 years age, by month, Australia and NSW**

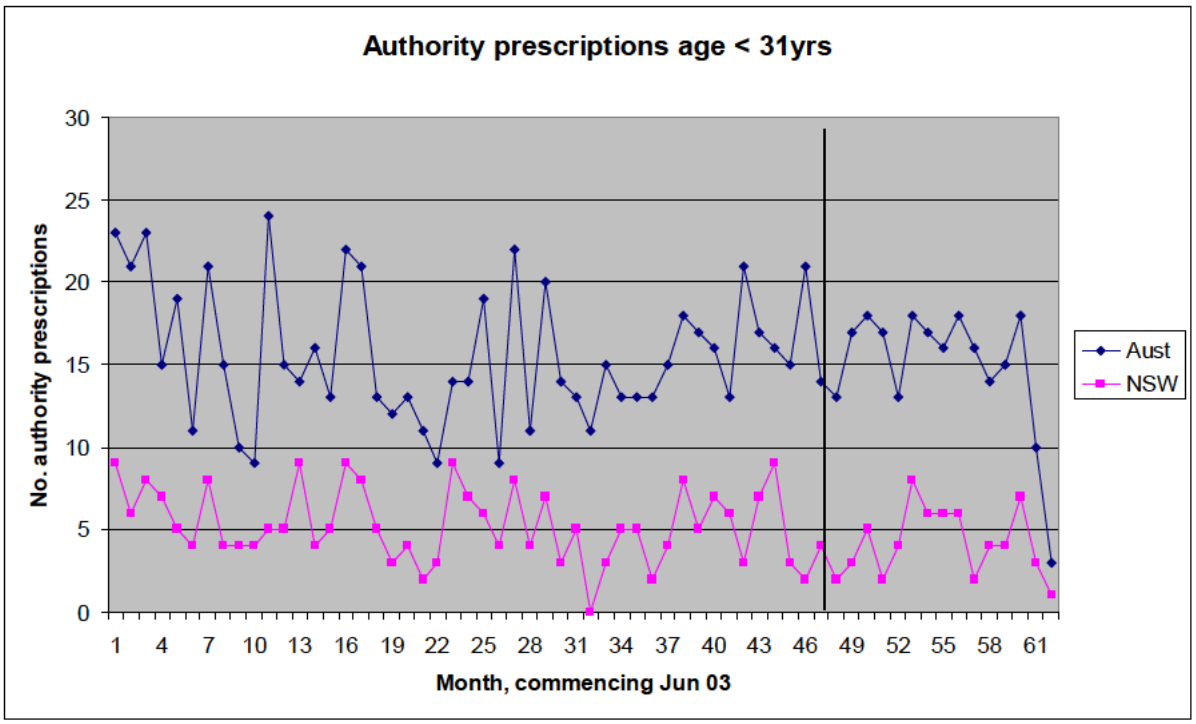

FIGURE FOUR **Authority prescriptions for MS immunomodulatory agents in female patients < 15 years age, by month, Australia and NSW**

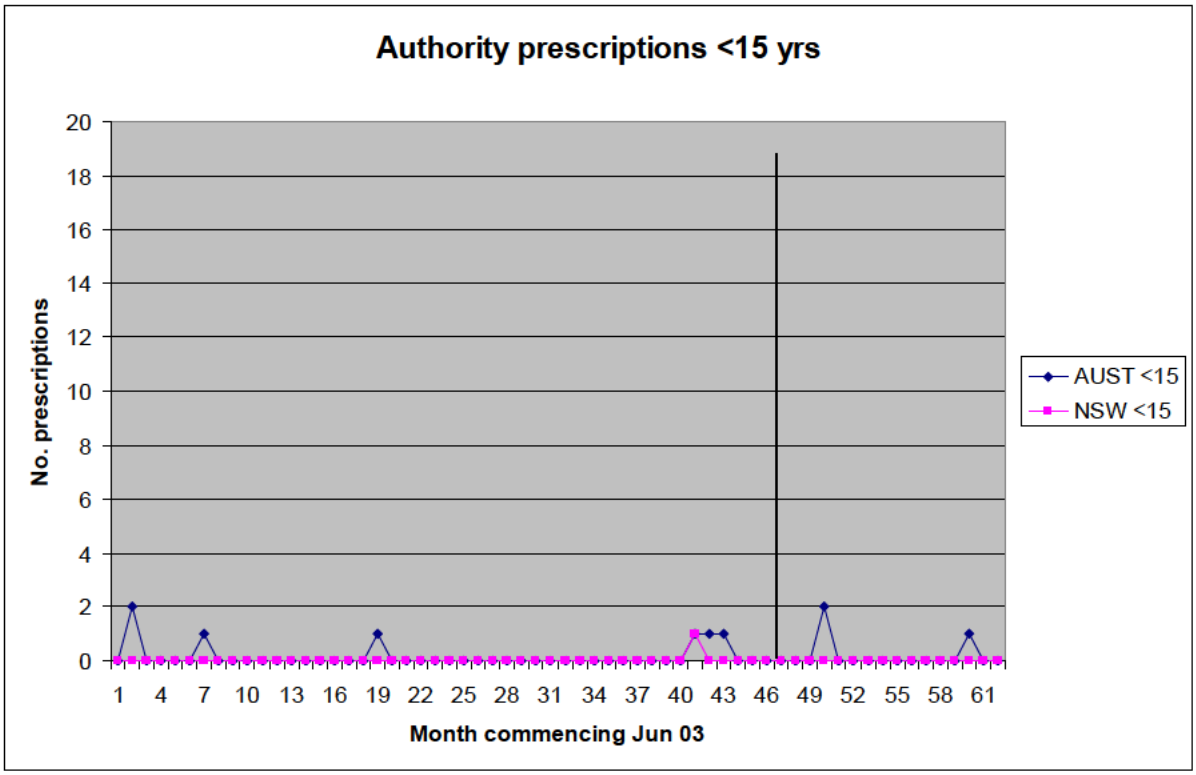

FIGURE FIVE **Authority prescriptions for MS immunomodulatory agents in female patients 15 to 25 years age, by month, Australia and NSW**

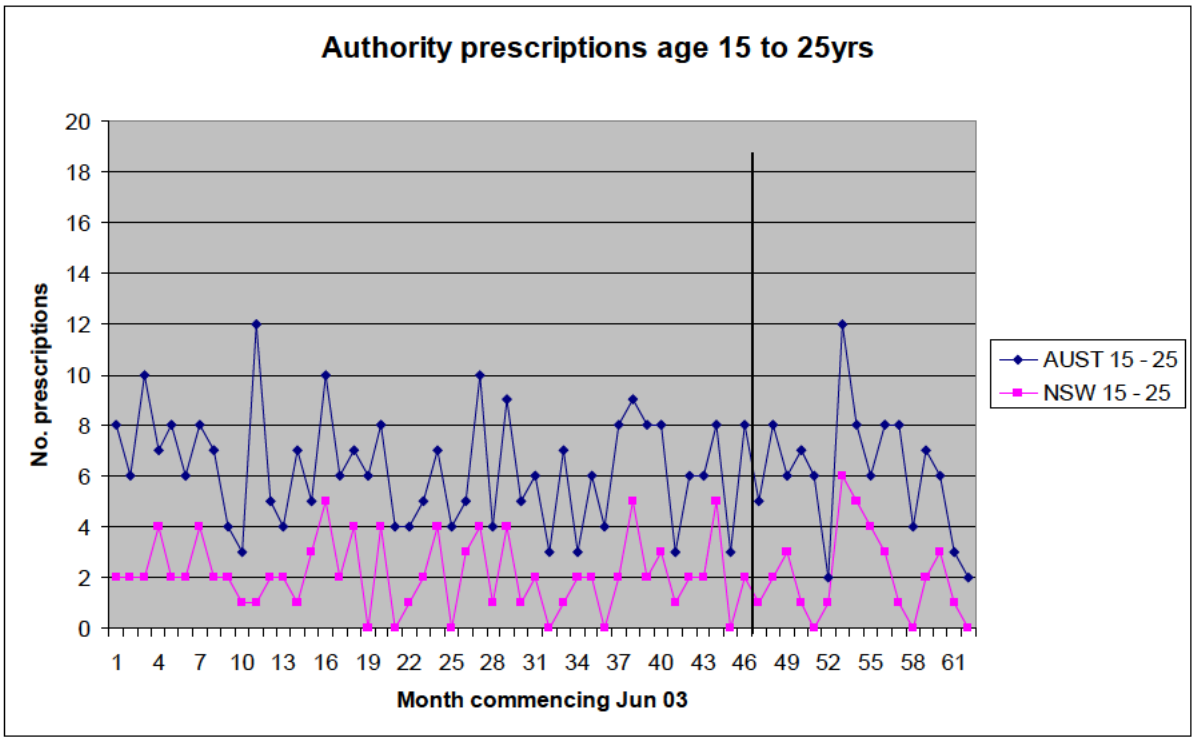

FIGURE SIX **Authority prescriptions for MS immunomodulatory agents in female patients 25 to 30 years age, by month, Australia and NSW**

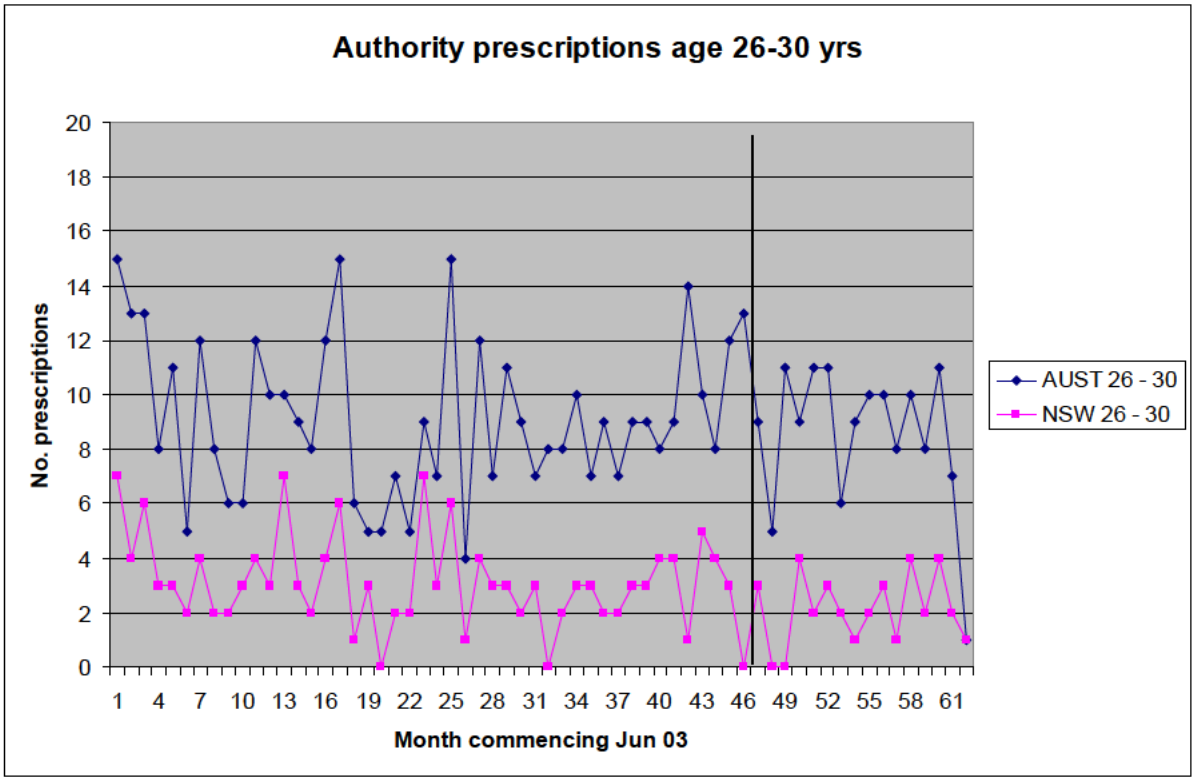

FIGURE SEVEN **New onset Type 1 Diabetes in females in Australia (NDSS data)**

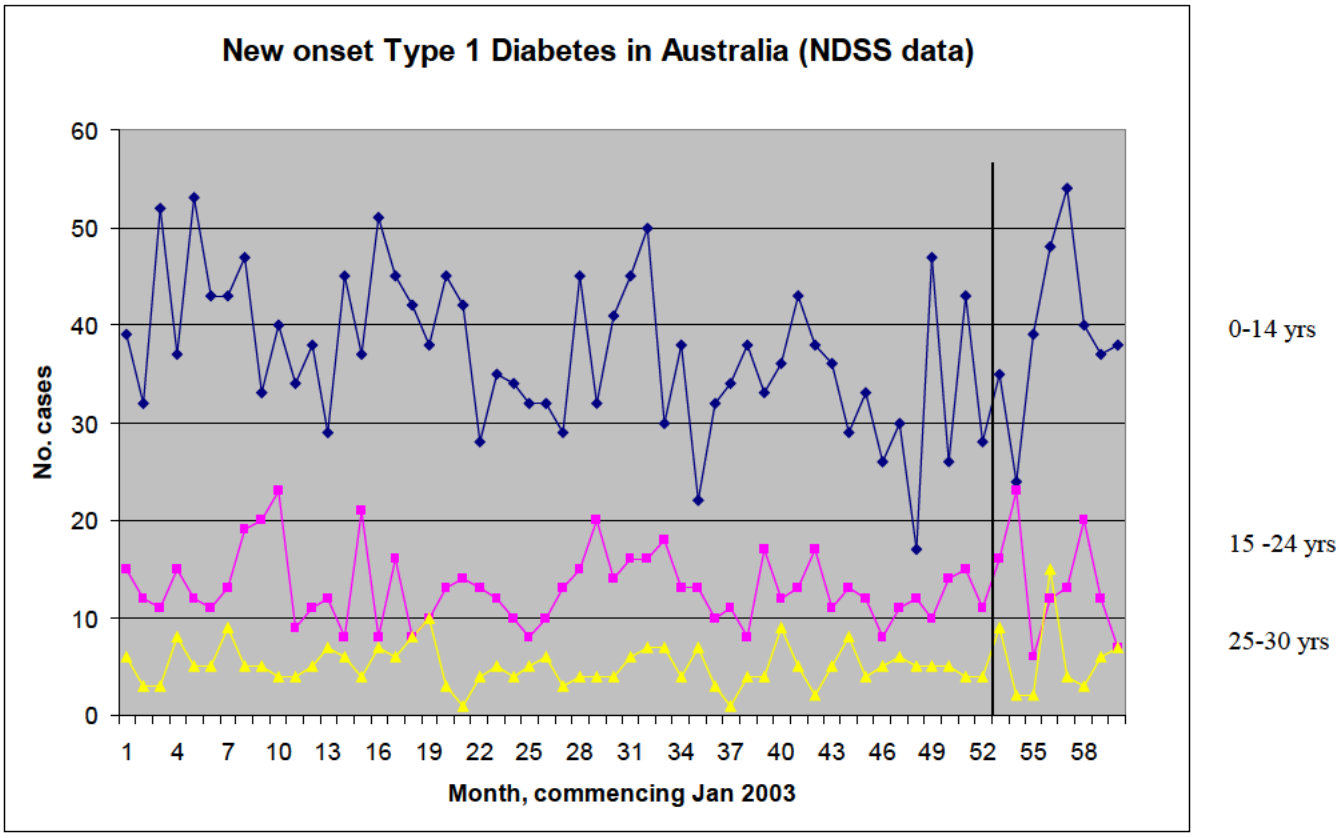

FIGURE EIGHT **New onset Type 1 Diabetes in females in NSW (NDSS data)**

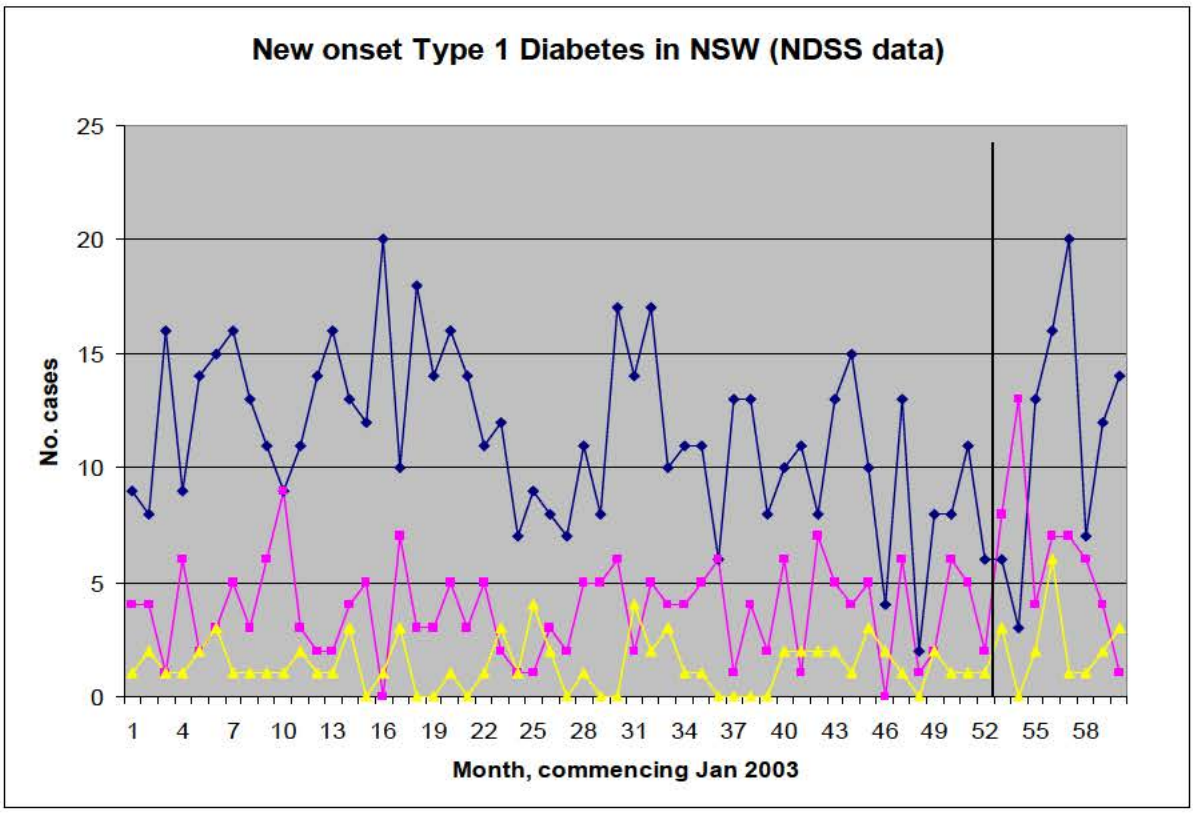

FIGURE NINE **New onset Type 1 Diabetes in females in Victoria (NDSS data)**

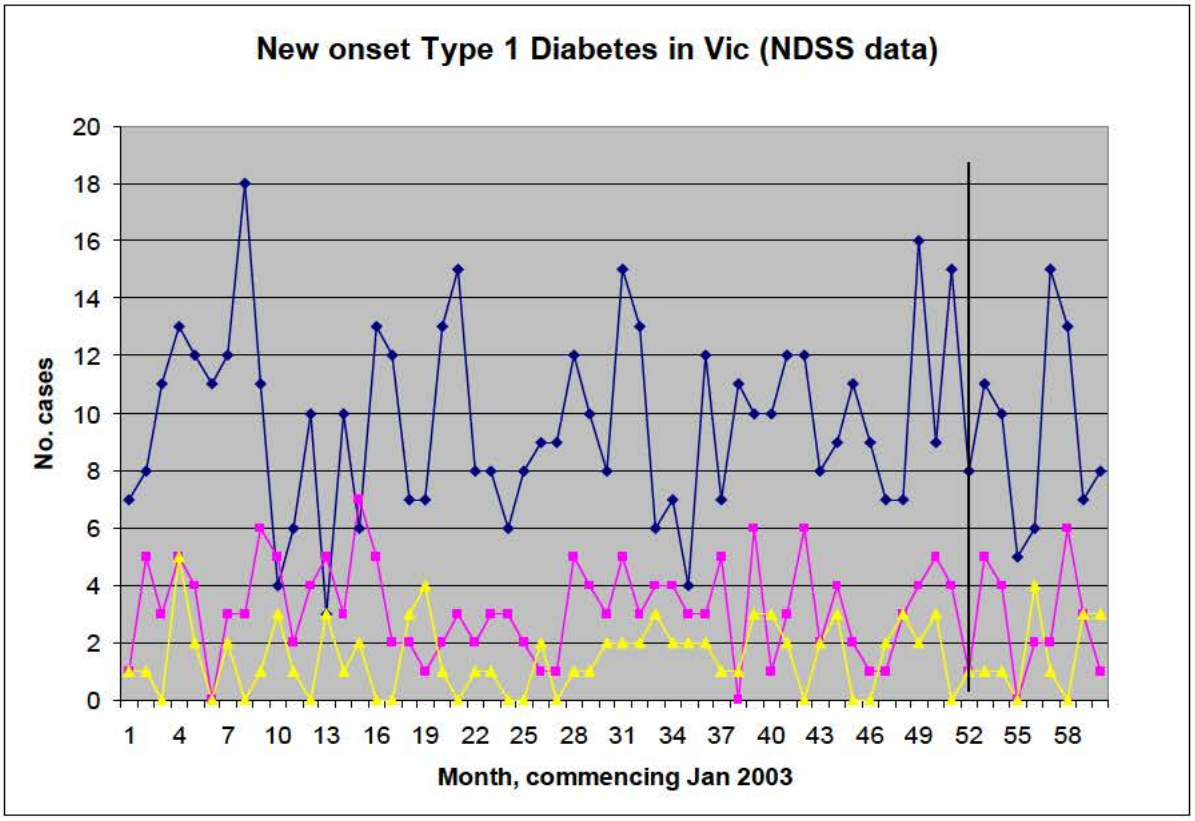

TABLE THIRTY TWO A Gardasil RMP - Action plans for important identified risks

Safety concern/issue	Planned activities	Detail/objective of measures	Additional notes/ Panel comment
• Exposure during pregnancy Inadvertent exposure during pregnancy	a. Enhanced pharmacovigilance	Standard operating procedures as part of an intensified effort to obtain follow up information regarding outcomes of exposure. Summary and review of exposure outcomes to be included in PSURs.	Current approved Product Information advises the vaccine should not be used in pregnancy. TGA condition of registration requires submission of annual U.S. Registry reports. Second annual report received by TGA as part of 2008 submission. Overall, the planned activities are comprehensive and appropriate
	b. Pregnancy registry (US, France, Canada)	Establishment and use of pregnancy register as a form of enhanced surveillance program for women exposed to Gardasil within 1 month of becoming pregnant or anytime during pregnancy	
	c. Surveillance Program (P031)	Observational study in Managed Care Organisation. The outcome of pregnancy exposures will be examined and the descriptive epidemiology summarised.	
	d. Vaccine in Population (VIP) study (P033)	VIP study will use the vaccine registry in conjunction with already established medical birth registries in 4 Nordic countries. Standardised incidence ratio of congenital abnormalities will be calculated by comparing observed and expected cases in women with inadvertent exposure during pregnancy.	
• Medical device malfunction Premature activation of safety shield used to prevent needle stick injury	a. Routine pharmacovigilance	Sponsor will receive, monitor and investigate reports as required	Sponsor investigation revealed this issue is related to end user inexperience. Product Information has been updated. The plan for ongoing monitoring and further clarification for end-users, where necessary, is appropriate
	b. Product Information	If needed, further clarification of instructions for use of safety shield will be included in the Product Information.	
• Hypersensitivity	a. Routine pharmacovigilance	Monitoring of spontaneous adverse events, including analysis and reporting in PSURs annually for three years post approval	The current approved PI includes contraindications for patients with hypersensitivity to any component of the vaccine. Also advises against further administration if patient develops de novo symptoms of hypersensitivity
	b. Product Information	Update product Information as appropriate to clearly communicate new information that arises	

TABLE THIRTY TWO B Gardasil RMP - Action plans for important potential risks

Safety concern/issue	Planned activities	Detail/objective of measures	Additional notes/ Panel comment
• Viral type replacement Theoretical concern - Gardasil targets only 4 of the many HPV types that infect the genital tract & HPV-type replacement could occur with widespread use	Nordic Long- term Follow-up study	Long term follow-up of women vaccinated in Protocol 015 will include surveillance for HPV-type specific disease, diagnosed by thin slice PCR. Analyses will be completed very two years through 2107, starting from last patient put in 2007	This measure is appropriate
• Guillain Barré Syndrome GBS may involve a non-specific immune stimulus	a. Routine pharmacovigilance	Monitoring of number of cases GBS in spontaneous reporting. Summary and review of cases to be included in PSURs	GBS has been added to the approved Product Information.
	b. Surveillance Program (P031)	Observational study in Managed Care Organisation. Cases will be evaluated by experts in the field.	
	c. PGRx Study	Use of case-control studies performed in the PGRx database for surveillance of autoimmune diseases in French patients	
	d. Product Information	Updating of Product Information as further information becomes available	
• Conditions of Special Interest Disorders of interest include MS, ADEM and optic neuritis	a. Routine pharmacovigilance	Monitoring of spontaneous adverse events, including analysis and reporting in PSURs annually for three years post approval.	Use of epidemiological studies is warranted and appropriate. However, PGRx protocol yet to be finalised (expected early 2009) with prospect of recruitment continuing over at least three years.
	b. Surveillance Program (P031)	Observational study in Managed Care Organisation with monitoring of potential signals related to autoimmune/rheumatologic conditions, including ITP, uveitis, type I diabetes mellitus, SLE, MS, ADEM, optic neuritis, Hashimoto's disease, Grave's Disease, among others	
	c. PGRx study	Use of case-control studies performed in the PGRx database for surveillance of autoimmune diseases in French patients	

TABLE THIRTY TWO C Gardasil RMP - Action plans for missing information

Missing information	Planned activities	Detail/objective of measures	Additional notes/ Panel comment
• Long term effectiveness and immunogenicity Duration of protection unknown at present	a. P018 extension	Protocol 018 extension will provide long term safety, immunogenicity and effectiveness data in 9 to 15 year old boys and girls. Immunogenicity and safety to be evaluated through ~3 years after enrolment with additional 3 years to evaluate effectiveness for total study duration of 6 years (~5.5 years post dose 3)	These measures are appropriate. The TGA has received follow-up data from P018 to month 30 as part of 2008 application. Noted that final reports will not occur until 2016/2017 but interim reports will be submitted to the TGA.
	b. Nordic Long- term Follow-up study	Long term data will be examined longitudinally. Endpoints will include cervical disease, VIN 2/3 and vulvar cancer, VaIN2/3 and vaginal cancer caused by vaccine HPV types (breakthrough disease) and replacement HPV types	
• Long term safety	Nordic Long- term Follow-up study	Long term follow-up of women vaccinated in Protocol 015. Analyses will be completed very two years through 2107, starting from last patient put in 2007	
• Unanticipated safety signals Detection of rarer events which only become evident with use in large numbers of people	a. Routine pharmacovigilance	Monitoring of spontaneous adverse event reports	These measures appear appropriate
	b. Surveillance Program (P031)	Monitoring of short term safety profile in Managed Care Organisation – particularly for rarer events undetectable in clinical trial programs, with updating of product information when necessary	
	c. Nordic Long- term Follow-up study	Monitoring of long term safety with updating of product information when necessary	

TABLE THIRTY THREE Target number of cases in proposed PGRx database case control studies

Condition	Target number of cases	Number of cases identified from Feb 2008 to July 22 2008
CNS Demyelination/multiple sclerosis	75	26
Lupus	60	5
Polyarthritis	30	5
Myositis/Dermatomyositis	15-30	-
Guillain Barré Syndrome	9-15	2
Type 1 diabetes	30-60	2
Autoimmune thyroiditis	15-30	-
Grave's Disease	15-30	3
ITP	30-45	5