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Department of Health

Therapeutic Goods Administration

Enhanced school-based surveillance of acute adverse events following immunisation with human papillomavirus vaccine in males and females, 2013

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TGA Health Safety
Regulation

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List of abbreviations

AEFI	Adverse event following immunisation
ATAGI	Australian Technical Advisory Group on Immunisation
GP	General practitioner
HPV	Human papillomavirus
MedDRA	Medical Dictionary for Regulatory Activities
NIP	National Immunisation Program
PI	Product Information
TGA	Therapeutic Goods Administration
VAERS	Vaccine Adverse Event Reporting System (United States)

1. Executive summary

Australia was the first country to introduce a government-funded National Human Papillomavirus (HPV) Vaccination Program for females. From 2007 to 2012, the TGA captured national adverse event reports via routine passive surveillance. In 2013, the National Immunisation Program (NIP) schedule was extended to include males (12 to 13 years as standard and a two year catch-up program for males aged 14 to 15 years), with the quadrivalent HPV vaccine, Gardasil continuing to be used in the extended program. The HPV Implementation Ad-hoc Working Group of the Australian Technical Advisory Group on Immunisation (ATAGI) recommended several enhanced surveillance activities to monitor adverse events following the commencement of the extended program in February 2013.¹

In collaboration with the state and territory health departments, the TGA implemented rapid surveillance and weekly feedback to the Jurisdictional Immunisation Coordinators and Immunisation Branch of the Office of Health Protection for the following four significant acute adverse events following immunisation (AEFIs) of special interest:

- anaphylaxis
- generalised allergic reaction
- loss of consciousness of any duration (syncope or seizure)
- any condition that required an emergency department presentation or hospitalisation.

This report describes all AEFIs reported to the TGA for quadrivalent HPV vaccine in 2013, including reports made through the enhanced surveillance arrangements, which focused on the four AEFIs of special interest above.

A search of the Australian Adverse Drug Reaction Reporting System for the period 1 January 2013 to 31 December 2013 identified 748 adverse event case reports following HPV vaccination that satisfied the inclusion criteria. Reporting rates per 100,000 HPV vaccine doses administered were calculated for AEFIs using data from the National HPV Vaccination Program Register. Reporting rates were calculated for males aged 12 to 13 years, females aged 12 to 13 years and males aged 14 to 15 years.

Overall, rates of reported AEFIs were higher among females aged 12 to 13 years (122 per 100,000 doses of HPV vaccine administered) than males aged 12 to 13 years (101 per 100,000 doses), while the rate of reported AEFI for males aged 14 to 15 years was approximately half the reported rate of the younger male group (44 per 100,000 doses).

No safety concern in females or males was identified. The types and reporting rates of AEFIs for males and females were consistent with information on these adverse events in the Gardasil Product Information (PI) and reported in clinical trials.²

Overall, the results from the first year of enhanced surveillance of acute adverse events following HPV vaccination in schools affirm the positive benefit-risk profile of HPV vaccination.

2. Background

The two human papillomavirus (HPV) vaccines registered for use in Australia are the bivalent vaccine, Cervarix, and the quadrivalent vaccine, Gardasil. Both vaccines protect against infection with the high-risk HPV types 16 and 18, while Gardasil also protects against the low-risk HPV types 6 and 11 and thereby provides additional protection against genital warts. Both vaccines are listed under the National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No. 1) for females, but only Gardasil is listed for use in males.

In April 2007, Australia became the first country to introduce a government-funded [National HPV Vaccination Program](#), which was implemented as part of the National Immunisation Program (NIP) and funded under the [Immunise Australia Program](#), a joint Australian, State and Territory Government initiative to increase immunisation rates for vaccine-preventable diseases.

The National HPV Vaccination Program is an ongoing school-based program that was initially delivered to 12 to 13 year old females. In 2007 to 2009, a two year catch-up program was delivered for 13 to 18 year old females in schools, and for 19 to 26 year old females through general practice and community-based programs. During 2007 to 2009, an estimated 83% of females aged 12 to 17 years received at least one dose of HPV vaccine and 70% completed the three-dose HPV vaccination course. Gardasil is the HPV vaccine being used in the National HPV Vaccination Program.

As expected, and as seen with other new population-wide vaccination programs, the number of HPV vaccine adverse events following immunisation (AEFIs) reported to the TGA was highest in the first year of the program and has then gradually declined. Current data held by the TGA indicates the annual number of reports in females has been stable over the three years prior to 2013.

A few weeks after the program was introduced in females, one school in Melbourne, Victoria, reported 26 cases of young adolescent females exhibiting symptoms that included dizziness, syncope (fainting) and neurological complaints. These symptoms occurred within a few hours of Gardasil administration and four cases required further medical review in a hospital emergency department. Despite a thorough investigation, no biological cause was found to explain the events and so this was considered a ‘mass psychogenic response’ to the vaccination process within that particular school environment.^{3,4} This event received local and international media interest.

Hypersensitivity reactions, including anaphylaxis, were identified in the months after the National HPV Vaccination Program was implemented, with initial concern that the rate of anaphylaxis was higher than expected.⁵ However, following investigation, the reporting rates for anaphylaxis and other serious allergic reactions following Gardasil vaccination were found to be consistent with other vaccines.^{6,7}

Syncope was also identified in the months after the National HPV Vaccination Program implementation. Although syncope is reported as an AEFI, it is generally regarded as being caused by the vaccination process. It is particularly common for younger adolescents to experience syncope in context of a painful stimulus. The reported rate of syncope for Victoria was evaluated retrospectively (7.8 per 100,000 HPV vaccine doses administered)⁸ and considered consistent with the reported rates for syncope reported in the United States (8.0 per 100,000)⁹, the Netherlands (10.0 per 100,000)¹⁰ and the United Kingdom (19.8 per 100,000: psychogenic events including syncope)¹¹.

In 2010, following the suspension of the use of bioCSL’s Fluvax in children, Professor John Horvath AO conducted the [Review of the management of adverse events associated with Panvax](#)

[and Fluvax](#) (the Horvath Review), which examined the reporting of, and responses to, both the management of the seasonal influenza vaccination program and the system for reporting of AEFIs with the purpose of identifying improvements that could be made to the Australian system for ensuring vaccines were used safely. While passive surveillance systems are valuable because they allow population-wide post-market monitoring of potential adverse events at relatively low cost, it is acknowledged they have limitations that may be supplemented in certain circumstances by other activities. The final Horvath Review report of 10 March 2011 included recommendations that related to the Australian vaccine safety system. These included the need for an improved system of governance for vaccine safety monitoring in Australia and for AEFIs to be reported in a timely manner.¹² As part of improved governance, an expert advisory committee for vaccine safety, the Advisory Committee on the Safety of Vaccines, has been established.

Following the recommendation of the Pharmaceutical Benefits Advisory Committee in November 2011 to include HPV vaccine for males within the NIP schedule, and the Australian Government decision to fund it, the Australian Technical Advisory Group on Immunisation (ATAGI) HPV Implementation Ad-hoc Working Group (the HPV Working Group) was established in 2012 to develop an enhanced surveillance program to coincide with the roll-out of HPV vaccination in males from February 2013.

The HPV Working Group noted that, although Gardasil had been administered to males in clinical trials, it had not been provided to males in the population in any large numbers, hence there were no data on expected types and rates of adverse events following routine HPV vaccination of Australian adolescent males. However, there were no biological or theoretical reasons to suggest the safety profile of Gardasil in males would be different to what had been reported for females. This was supported by clinical trial data and preliminary passive post-marketing data from the USA.¹

The HPV Working Group developed a plan for the monitoring and review of potential adverse events associated with the extended National HPV Vaccination Program in males. The planned activities and recommendations were aligned with those detailed in the Horvath Review. The HPV Working Group proposed that state and territory school-based vaccination teams gather information on acute significant AEFIs that occurred at school on the day of vaccine administration, irrespective of whether the AEFI was determined to be causally or coincidentally related to vaccination.

The HPV Working Group recommended that the information obtained should be analysed at regular intervals and ultimately reported to the public in order to maintain public and immunisation provider confidence in the program. They also considered it important that data on an agreed set of acute significant adverse events following immunisation with Gardasil be collected by state and territory health departments and forwarded to the TGA daily.

The acute significant adverse events, referred to as adverse events of special interest, included those that occurred immediately or shortly after vaccination, and were either observed or reported to the school-based vaccination team. The adverse events recommended for surveillance were:

- anaphylaxis
- generalised allergic reaction
- loss of consciousness of any duration (syncope or seizure)
- any condition that required emergency department presentation or hospitalisation.

The HPV Working Group developed case definitions for these adverse events for the vaccination teams to use to decide what to report (see Annex A).

All symptoms and signs were to be recorded for each case. The management of each case was also to be documented (for example: if adrenaline was administered, the number of doses; administration of other treatment such as oxygen; if transfer to emergency department occurred; and follow-up management in emergency department).

The HPV Working Group advised that the numbers of events should be reviewed and vaccine usage data requested from the state and territory programs to determine if the reported rate of significant acute AEFIs was higher than anticipated.

A collaborative group from the TGA, the Immunisation Branch of the Office of Health Protection and the state and territory Jurisdictional Immunisation Coordinators adopted the HPV Working Group recommendations and implemented an enhanced passive surveillance program of HPV AEFI in February 2013.

The enhanced surveillance activities implemented for the extension of HPV vaccination to males also had the potential to monitor for rare adverse event signals that are generally not captured through pre-marketing clinical trials and purely spontaneous adverse event reporting due to their low incidence. In the enhanced surveillance program, specific adverse events were targeted and immunisation providers were also requested to report all adverse events of which they became aware. While it has advantages over a purely spontaneous adverse event reporting system, it will not necessarily reflect the actual rate of adverse event occurrence that would occur with an active surveillance system (where all adverse events are systematically collected) or data linkage. The major advantages of the enhanced surveillance system were the targeting of certain adverse events and therefore higher reporting of the adverse event of interest; and the ability to collect and analyse national data early.

This enhanced surveillance added to the routine monitoring the TGA continued to perform through analysis of data relating to all adverse events following HPV vaccination from all sources, including spontaneous reports and information provided by state and territory health departments, health professionals, sponsors and consumers.

3. Methods

3.1 Case selection

3.1.1 Search strategy

3.1.1.1 Case reports

A search of the Australian Adverse Drug Reaction Reporting System for the period 1 January 2013 to 31 December 2013 using the search term 'human papillomavirus' identified 814 adverse event case reports. The reports were for Gardasil (659), HPV vaccine quadrivalent (61) and HPV vaccine unspecified (94). The unspecified cases were all administered to males and females in the age range for school-based vaccination and were assumed to be Gardasil.

Calendar year was selected, as it coincided with denominator data obtained from the National HPV Vaccination Program Register¹³ and captured all HPV vaccine doses administered in the 2013 school year for males aged 12 to 15 years and females aged 12 to 13 years. Adverse event reports that were received during this period, but were associated with vaccination prior to 1 January 2013 were excluded from the analysis (see 3.1.2.2 Exclusion criteria).

3.1.1.2 Adverse event terms

Each case report the TGA received included at least one adverse event (usually described as a sign or symptom). TGA staff with either medical or nursing qualifications reviewed the coding of reports and, where insufficient information had been provided, requested additional information from the reporter of the adverse event.

The adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology, a standardised hierarchical regulatory adverse event-coding system. Specifically, adverse events were coded using MedDRA Lower Level Terms, but were analysed using MedDRA Preferred Terms. Some of the adverse events of special interest defined for enhanced surveillance by the HPV Working Group (for example generalised allergic reaction and emergency department presentation) could not be captured by MedDRA Preferred Terms, requiring the creation of specific categories for this report. Throughout this report, 'reaction term' is used to capture both MedDRA and non-MedDRA coded terms.

The specific category of 'generalised allergic reaction' created for and used in this report has three subcategories:

- *urticaria*
- *hypersensitivity* – which captures all cases listed as 'allergic reaction' which did not meet the case definition for anaphylaxis
- *other generalised allergic reaction* – which captures all cases coded as swelling (facial, tongue or pharyngeal); throat irritation and throat tightness; and bronchospasm or wheezing.

Localised allergic reactions, which include pruritus and pruritic rash, are reported separately.

Afebrile seizures were coded to 'convulsion'.

Syncopal seizures were coded to 'syncope'.

3.1.2 Inclusion and exclusion criteria

Consistent with current data analysis methodology, all Gardasil adverse event reports were included irrespective of whether HPV vaccine was administered as a single vaccine or co-administered with other vaccines. Hence, the AEFI rates reported here are likely to overestimate true rates for Gardasil.

Cases were included if they fully met the inclusion criteria below.

It was not possible to separate the cases reported via the enhanced surveillance program from spontaneous reports the TGA received from other sources. Therefore, all cases that met the inclusion criteria were included in the analysis.

3.1.2.1 Inclusion criteria

- a male aged 12, 13, 14 or 15 years and females aged 12 or 13 years
- a male or female with an onset of an adverse events(s) after 1 January 2013 and before 31 December 2013
- a male or female who had an adverse event(s) reported after their first, second or third prescribed dose of Gardasil
- missing sex (male or female) alone did not exclude a case being included in the primary analysis
- the reported adverse event(s) is biologically plausible and/or there is a temporal association with the administration of HPV vaccine.

Note: missing state or territory data alone did not exclude a case being included in the primary analysis.

3.1.2.2 Exclusion criteria

- a male or female aged less than 12 years
- a male aged more than 15 years or a female aged more than 13 years
- a male or female of indeterminate age
- a male or female with an onset of an adverse events(s) before 1 January 2013 or after 31 December 2013
- a male or female with an indeterminate onset date of an adverse event(s)
- a male or female who had a vaccination schedule error, such as more than the three scheduled Gardasil doses
- the reported adverse event(s) is biologically implausible or the temporal association with the administration of HPV vaccine is unclear, i.e. the onset of the adverse event has not been provided.

3.2 Inter-agency collaboration

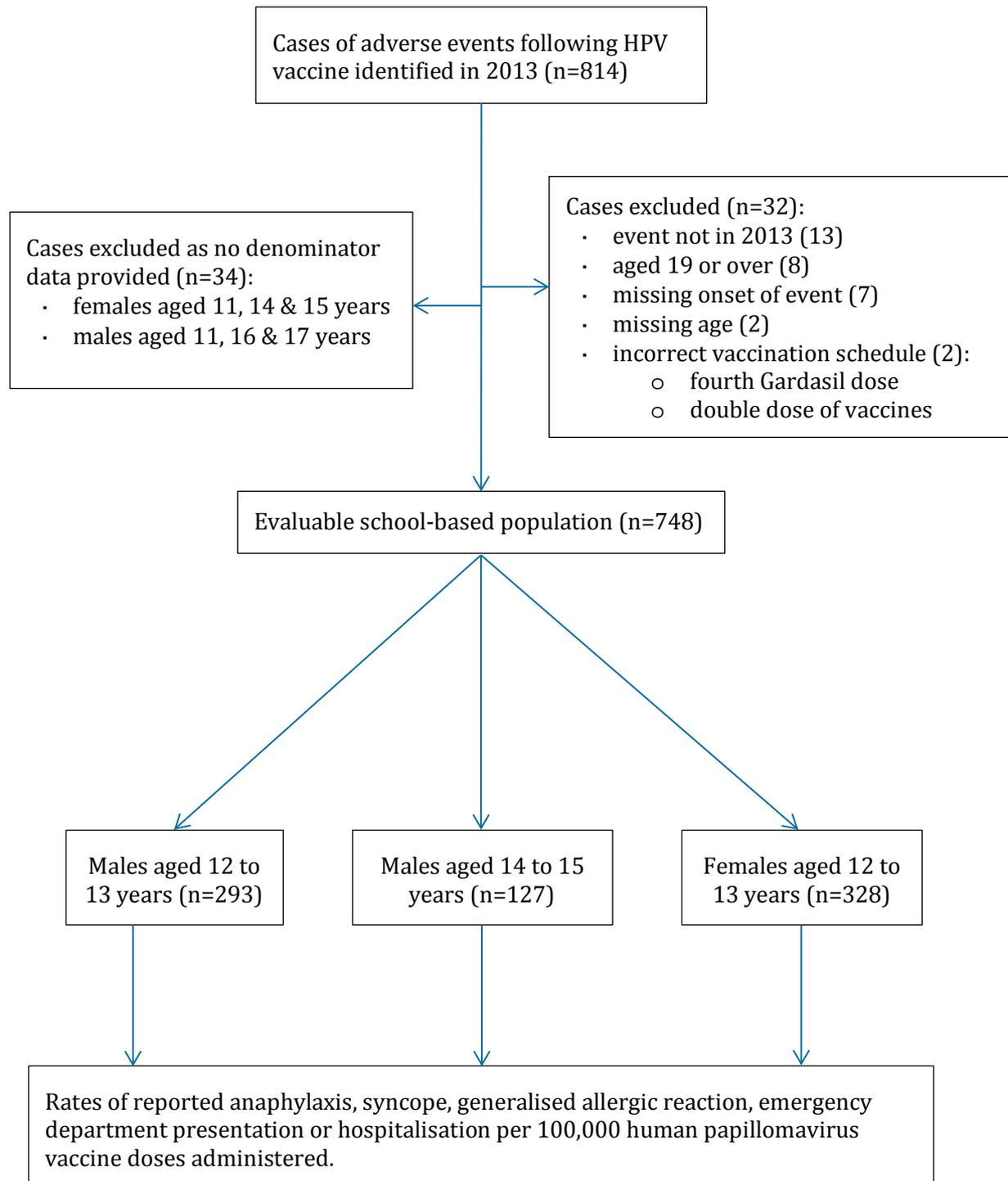
The enhanced surveillance activities undertaken from the commencement of the school program in February 2013 included:

- request by state and territory jurisdictions for immunisation providers in schools to report adverse events of special interest to them daily
- daily reporting of these adverse events from the state and territory jurisdictions to the TGA
- daily review of each HPV vaccine-related adverse event case report received at the TGA by a trained nurse or medical officer (review included coding of the adverse event and request for further information)
- weekly collation of HPV vaccine-related adverse events received by the TGA
- a weekly (later monthly) teleconference between the TGA, Immunisation Branch and Jurisdictional Immunisation Coordinators to review the HPV vaccine adverse event case reports received the previous week, and cumulative reports for 2013.

For other AEFIs, the normal spontaneous reporting system remained in place. These spontaneous reports were also provided to the Jurisdictional Immunisation Coordinators.

3.3 Flow diagram

Cases analysed in this report (Figure 1) are assumed to relate to scheduled Gardasil doses received at school, irrespective of where the vaccinations were actually received. Cases have been included regardless of whether they were reported via the enhanced surveillance program or via the TGA's routine spontaneous reporting system.

Figure 1: Flow diagram

3.4 Analyses

Results are presented as descriptive statistics. All date ranges are inclusive.

3.4.1 Population definition

This report included analyses for the evaluable school-based population, which comprised all cases that met the inclusion criteria and for which denominator data were provided from the National HPV Vaccination Program Register.

3.4.2 Denominator data

Denominator data for the calculation of case report and AEFI rates were the number of HPV vaccine doses administered between 1 January 2013 and 31 December 2013, as reported to the National HPV Vaccination Register before 16 April 2014. Data were provided by the Register by sex, age and state or territory (Annex B).

Denominator data were provided for the following age-groups* in 2013:

- females aged 12 to 13 years
- males aged 12 to 13 years
- males aged 14 to 15 years.

Although these age groups do not completely align with the school-year groups vaccinated in each state and territory (Annex D), only a small number of reports (34) were for cases with ages outside these groups and absence of data for the other ages was not expected to significantly change the age-specific or national rates.

Rates of case reports per 100,000 HPV vaccine doses administered for the period 1 January 2013 to 31 December 2013 are presented by sex, age and by state or territory in Table 1 below. The numbers of adverse event case reports received for the period 1 January 2013 to 31 December 2013 are presented by sex, and by state or territory in Annex C (Table A).

3.4.3 All adverse events following immunisation

Although the enhanced surveillance program was focused on collecting reports of adverse events of special interest, the TGA continued to collect reports of all AEFIs.

Reported AEFI rates per 100,000 HPV vaccine doses administered are presented for the top 10 ranked reaction terms in Table 2 below. Reported numbers of all adverse events following HPV vaccine administration are presented by reaction term, sex and age in Annex C (Table B).

3.4.4 Adverse events of special interest

Reported rates per 100,000 HPV vaccine doses administered were calculated for the following adverse events of special interest:

- anaphylaxis
- generalised allergic reaction (Table 3), which included:
 - urticaria

* Age at first dose of HPV vaccine

- hypersensitivity
- other generalised allergic reaction.
- loss of consciousness (Table 4), which included:
 - simple syncope
 - syncopal seizure
 - syncope with injury.
- emergency department presentation or hospitalisation (Table 5).

The numbers of adverse events following HPV vaccination by sex and age are presented for generalised allergic reaction, syncope and emergency department presentation or hospitalisation in Annex C (Tables C, D and E, respectively).

4. Results

4.1 Overall rates of case reports of adverse events following HPV immunisation

The overall rate of case reports of AEFI was 88.2 case reports per 100,000 HPV vaccine doses administered. Rates were higher among females than males in the 12 to 13 years age group, while the rate for males aged 14 to 15 years was approximately half the rate of the younger male group (Table 1).

Based on population size, the ACT had the highest sex- and age-specific rates of case reports of AEFI (Table 1).

Table 1: Rates of case reports of adverse events following immunisation per 100,000 human papillomavirus vaccine doses administered, by sex, age and state and territory

Sex	Age (years)	ACT	NSW	NT	QLD	SA	TAS	VIC	WA	Australia
Male	12 to 13	732	108	26	100	0	131	95	21	101
	14 to 15	411	31	75	40	31	0	48	39	44
Female	12 to 13	915	129	89	114	76	67	89	0	122

4.2 Rates of the most frequently reported adverse events following HPV immunisation

Females had higher rates of reported AEFI than both male age-groups, except for pyrexia, for each of the 10 top ranked reaction terms (Table 2), which are derived from the more detailed list in Annex C, Table B. Females had approximately twice the AEFI rate for presyncope compared with males aged 12 to 13 years and four times the rate for males aged 14 to 15 years. Males aged 14 to 15 years had the lowest AEFI rates for each of the top 10-ranked AEFIs (Table 2).

Table 2: Rates of the ten most frequently reported adverse events following immunisation per 100,000 human papillomavirus vaccine doses administered, by reaction term, age and sex

Reaction term	Males 12 to 13 years	Males 14 to 15 years	Females 12 to 13 years	All
Syncope#	48.2	14.2	49.5	37.0
Presyncope	8.3	4.5	15.6	9.3
Rash	8.3	3.8	11.9	7.9
Headache	7.2	6.9	9.3	7.9
Injection site reaction*	6.2	4.5	12.7	7.7
Nausea	8.3	3.8	10.8	7.5
Dizziness	8.3	2.8	11.5	7.4
Generalised allergic reaction**	6.5	6.6	8.2	7.1
Pyrexia	7.6	5.2	6.7	6.5
Vomiting	4.8	2.8	7.8	5.1

includes syncopal seizures

* includes pain, swelling, erythema, rash and unspecified reaction at the injection site

** includes urticaria, hypersensitivity and other generalised allergic reaction

4.3 Adverse events of special interest

4.3.1 Anaphylaxis

One 14 year old male with a history of unstable asthma was diagnosed with anaphylaxis according to the definition in Annex A which was adapted from the Brighton Collaboration case definition.¹⁴ This represented an overall reported event rate of 0.12 per 100,000 HPV vaccine doses administered or 0.35 per 100,000 HPV vaccine doses administered for males aged 14 to 15 years.

4.3.2 Generalised allergic reaction

Overall rates of reported generalised allergic reaction events were comparable between males aged 12 to 13 years and males aged 14 to 15 years. In contrast, females aged 12 to 13 had a higher rate (Table 3). Urticaria accounted for almost half the generalised allergic reactions. Males tended to have more events of urticaria than females. Younger males tended to have more

hypersensitivity events than the other age-groups. Females tended to have more other generalised allergic reaction events than males.

Table 3: Rates of reported generalised allergic reactions per 100,000 human papillomavirus vaccine doses administered, by reaction term, age and sex

Reaction term	Males 12 to 13 years	Males 14 to 15 years	Females 12 to 13 years	All
Urticaria	3.8	3.1	2.6	3.2
Hypersensitivity	1.4	0.7	0.7	0.8
Other generalised allergic reaction	1.7	2.8	4.8	3.1
Total	6.5	6.6	8.2	7.1

4.3.3 Loss of consciousness (syncope and seizure)

The rates of reported simple syncope, syncopal seizures and syncopal events resulting in injury post-vaccination were comparable between males and females aged 12 to 13 years and lower in males aged 14 to 15 years (Table 4). Only one case presented to emergency department or hospital for review of an injury (back pain) sustained as a result of syncope.

Table 4: Rates of reported syncope per 100,000 human papillomavirus vaccine doses administered, by age and sex

Reaction term	Males 12 to 13 years	Males 14 to 15 years	Females 12 to 13 years	All
Simple syncope	42.4	12.8	43.9	32.8
Syncopal seizure	5.9	1.4	5.6	4.2
Syncope with injury	2.1	0.7	3.0	1.9

In addition, five vaccine recipients, two males and three females aged 12 to 13 years, had a convulsion (afebrile seizure). Each case had a known history of convulsion.

4.3.4 Emergency department presentation or hospitalisation

The rates of events that resulted in presentation to an emergency department or hospital immediately after vaccination were comparable between males and females aged 12 to 13 years. In contrast, males aged 14 to 15 years had a lower rate of emergency department presentations or hospitalisations than younger males and females (Table 5).

Table 5: Rates of reported emergency department presentation or hospitalisation per 100,000 human papillomavirus vaccine doses administered, by age and sex

Reaction term	Males 12 to 13 years	Males 14 to 15 years	Females 12 to 13 years	All
Emergency department presentation or hospitalisation	6.9	1.7	5.2	4.6

The cases who presented to an emergency department or hospital for medical review included: nine cases of generalised allergic reaction (including the one case of anaphylaxis); six presyncope cases that required observation; five cases of convulsion (all with a known history of convulsions); five cases of simple syncope that required observation; two cases of anxiety and one case of syncope with acquired injury (back pain).

4.4 Inter-agency collaboration

Weekly teleconferences between the TGA, Immunisation Branch and Jurisdictional Immunisation Coordinators were conducted initially. After the first month it was decided to change to monthly inter-agency teleconferences, with provision to convene a meeting at short notice if required. When it became clear that there was no mass psychogenic response to HPV vaccination in males, and that very few syncopal episodes resulted in injury or required further medical review, a decision was made after the majority of first doses had been administered to cease the request for school-based reporting of simple syncope events. The request to report loss of consciousness related to more complex syncope (syncopal seizure and syncope with injury) or convulsion continued.

5. Discussion

5.1 Denominator data

Comparison of AEFI rates between countries, as well as Australian states and territories, may differ due to variations in reporting mechanisms, case definitions and rate derivation. Hence, caution should be exercised when interpreting results by geographical location. The ACT had a higher reporting rate of age- and sex-specific AEFIs that may be partly explained by the decision to continue collecting syncopal events. Furthermore, historically the ACT is known to have a high overall rate of reporting AEFIs. A review of ACT case reports did not identify any unexpected AEFIs or higher rates of serious AEFIs compared with other jurisdictions.

5.2 Rates of reported adverse events following HPV immunisation

Aside from syncope (see Section 5.3.3), the types and relative frequencies of AEFI identified in this report are consistent with the Gardasil Product Information (PI)², clinical trial data and previous information published by the TGA.¹⁵

The range and rates for AEFIs were consistent between males and females. However, males aged 14 to 15 years tended to have significantly lower rates of AEFIs than younger males and females.

5.3 Adverse events of special interest

5.3.1 Anaphylaxis

The rate of reported cases of anaphylaxis in this report is consistent with international rates reported for other vaccines given to children and adolescents.^{6,7}

5.3.2 Generalised allergic reactions

The overall rate for reported hypersensitivity of 0.8 events per 100,000 HPV vaccine doses administered reported here is lower than the rate of 3.1 events per 100,000 HPV vaccine doses reported in a US population by Slade et al.¹⁶ In contrast, the AEFI rate for urticaria in this report of 3.3 events per 100,000 HPV vaccine doses administered was similar to that reported by Slade et al (2.6 events per 100,000 vaccine doses administered).

5.3.3 Loss of consciousness (syncope and seizure)

Syncope was reported in 42% of the cases and accounted for approximately 26% of the total AEFIs in this report. This is in contrast to a United States study¹⁷ that reported syncope in 15% of cases and a TGA web statement which reported syncope in 8.6% of case reports, the majority of which were received prior to the commencement of the enhanced surveillance described in this report.¹⁵ The United States Vaccine Adverse Event Reporting System (VAERS) from June 2006 to December 2008 reported the rate of syncope as 8.2 events per 100,000 HPV doses administered.¹⁶ This contrasts with 32.8 uncomplicated syncope events per 100,000 HPV vaccine doses administered in this report. Fainting/syncope is not listed as a common adverse event observed in pre-marketing clinical trials in the Gardasil PI, but is included in the 'Precautions' and the 'Method of Administration' sections.²

It should be noted that syncope can follow any vaccination, especially in adolescents and young adults, and is associated with the vaccination event rather than the vaccine itself.

The higher numbers of reports of syncope received in 2013 were expected because immunisation providers were specifically asked to collect and report this event as part of this enhanced surveillance program. There was no evident mass psychogenic response to HPV vaccination as occurred when HPV vaccine was introduced into schools for Australian females in 2007.^{3,4} However, the similar higher rates for syncope for males and females aged 12 to 13 years compared with the lower rate for males aged 14 to 15 years suggests there may be a psychological component to mass vaccination of similar-aged children in a school environment.

Males aged 14 to 15 years had approximately a four-fold lower rate of reported syncopal seizures compared with younger males and females. This result suggests older males may have a greater tolerance to the pain and anxiety associated with the vaccination process than their younger peers. This effect, while untested, may be due to greater lifetime vaccination exposure or psychosocial effects such as peer pressure.

Given the number of reports of syncope, very few subjects received an injury post-vaccination (1.9 events per 100,000 HPV vaccine doses administered). Furthermore, only one case required further medical review in an emergency department or at hospital. This is in contrast to VAERS data for all vaccines between 2005 and 2007 which showed that 7% of syncopal episodes were classified as serious and 12% were further complicated with head injuries.¹⁸ Another study of VAERS data found 15% of syncopal episodes resulted in a fall, of which 68% resulted in a head injury.¹⁶ The results presented in this report provide reassurance that vaccine administrators are recognising syncope (and presyncope) early and acting in an appropriate manner to prevent the subject from sustaining an injury. However, it is important that those providing immunisations continue to understand the risk of syncope and how to prevent and manage it.

The five reported cases of generalised tonic-clonic seizures, each coded as 'convulsion', were afebrile in nature and occurred in subjects with a medical history of convulsion. All required further medical review and management.

5.3.4 Emergency department presentation or hospitalisation

Approximately 56% of cases who presented to an emergency department or hospital for medical review were from the adverse events of special interest categories.

5.4 Inter-agency collaboration

The joint decision to cease the request for school-based reporting of syncopal events was implemented in a timely and coordinated way. This demonstrated the flexibility of the enhanced surveillance program and indicated that it would be a suitable model to use for other vaccines newly listed on the NIP schedule and funded under the Immunise Australia Program. The regular monthly teleconferences are continuing between the agencies and have included monitoring of and discussion about nationally collated data for other newly listed vaccines.

5.5 Report limitations

According to data provided from the National HPV Vaccination Program Register, approximately 3.5% of total doses of HPV vaccine administered in 2013 were by general practitioners (GPs).¹³ Analysis to compare AEFI reported following GP administered vaccine compared with school-based administered vaccine was not undertaken as information on where the vaccine was administered is not uniformly included on AEFI reports or entered into the database.

Approximately half the evaluable school-based population received concomitant vaccines in addition to HPV vaccine. Hence, the AEFI rates reported here are likely to overestimate true rates for Gardasil.

6. Conclusions

This report did not identify any safety concern in females or males.

The types and reporting rates of AEFIs identified in this report, for both males and females, were consistent with the Gardasil PI and the previous information published on the TGA website. Males aged 14 to 15 years tended to have much lower AEFI rates than younger males and females.

Syncopal events in 2013 (especially in the first school term) were high, as expected, but no mass psychogenic response was evident. Following the decision to cease active reporting of syncopal events, except for those that resulted in injury or necessitated further medical review, the number of reports of syncope reduced and was even lower in 2014.

Applying a consistent, timely and coordinated approach to sharing vaccine-related data from the HPV enhanced surveillance activities has enabled the TGA, Immunisation Branch and state and territory health departments to put in place a mechanism to monitor adverse events closely, and to undertake early analysis, with the ability to undertake a timely, thorough investigation of a new safety signal with a coordinated approach should the need arise.

Overall, the results from the first year of enhanced surveillance of acute adverse events following HPV vaccination in schools affirm the positive benefit-risk profile of HPV vaccination.

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Annexes

Annex A – Case definitions

The HPV Working Group Report proposed case definitions to be used by the school-based vaccination teams to collect data for reporting the adverse events of special interest recommended for the enhanced surveillance program for HPV vaccination.¹

The case definitions used for reporting are described below. The case definitions used for the coding and analysis of the data are described in the body of this report.

Anaphylaxis

A hypersensitivity reaction characterised by:

- sudden onset AND
- rapid progression of signs and symptoms AND
- involvement of multiple (≥ 2) organ systems AND
- with at least one symptom or sign of respiratory and/or cardiovascular involvement.

This definition is simplified and adapted from the Brighton Collaboration case definition of anaphylaxis.¹⁴

Generalised allergic reaction

A non-anaphylactic, generalised reaction characterised by one or more signs and symptoms of skin and/or gastrointestinal tract involvement WITHOUT respiratory or cardiovascular involvement.

This category is designed to capture vaccine recipients who experience a significant allergic reaction that has its onset immediately or shortly after (for example less than four hours) vaccination, but who do not meet the criteria for anaphylaxis.

It does not include minor redness and/or itchiness at the injection site.

Loss of consciousness of any duration (syncope or seizure)

Unconsciousness (resulting from a 'loss of consciousness') is a state of impaired consciousness often resulting in a loss of posture during which one shows no response to environmental stimuli but may respond to deep pain with involuntary movements. Loss of consciousness in this context can be due to syncope or seizure (either a syncopal seizure or a convulsion).

Emergency department presentation or hospitalisation

This category includes any condition that required a presentation to an emergency department or admission to hospital, for further medical review or management of their condition.

Annex B – Number of doses of human papillomavirus vaccine administered

Table A: Doses of human papillomavirus vaccine administered between 1 January 2013 and 31 December 2013 by sex, age and state or territory

Sex	Age group	ACT	NSW	NT	QLD	SA	TAS	VIC	WA	Australia
Male	12 to 13 years	5052	90,029	3811	66,088	2256	6114	79,808	37,234	290,392
	14 to 15 years	4376	78,003	2652	57,206	19,188	5541	70,395	51,324	288,685
Female	12 to 13 years	5029	85,541	3355	70,007	20,942	4466	78,299	1010	268,649
Total		14,457	253,573	9818	193,301	42,386	16,121	228,502	89,568	847,726

Source: National HPV Vaccination Program Register: data provided as at 16 April 2014

Age is at first dose of HPV vaccine

State and/or territory is based on the consumer's address on 16 April 2014

Excludes consumers who do not wish their details to be recorded on the HPV Register

Annex C – Number of adverse event case reports received for human papillomavirus vaccination

Table A: Number of adverse event case reports received following human papillomavirus vaccination by sex, age and state and territory (1 January 2013 to 31 December 2013)

Sex	Age group	ACT	NSW	NT	QLD	SA	TAS	VIC	WA	Australia
Male	12 to 13 years	37	97	1	66	0	8	76	8	293
	14 to 15 years	18	24	2	23	6	0	34	20	127
Sub-total		55	121	3	89	6	8	110	28	422
Female	12 to 13 years	46	110	3	80	16	3	70	0	328
Total		101	231	6	169	22	11	180	28	748

Table B: Numbers of reported acute adverse events following human papillomavirus vaccination, by reaction term, age and sex (1 January 2013 to 31 December 2013)

Reaction term	Males 12 to 13 years [n (%)]	Males 14 to 15 years [n (%)]	Females 12 to 13 years [n (%)]	Total [n (%)]
Syncope#	140 (31.7)	41 (16.4)	133 (25.6)	314 (25.9)
Presyncope	24 (5.4)	13 (5.2)	42 (8.1)	79 (6.5)
Rash†	24 (5.4)	11 (4.4)	32 (6.2)	67 (5.5)
Headache	21 (4.8)	20 (8.0)	25 (4.8)	66 (5.4)
Injection site reaction*	18 (4.1)	13 (5.2)	34 (6.5)	65 (5.4)
Nausea	24 (5.4)	11 (4.4)	29 (5.6)	64 (5.3)
Dizziness	24 (5.4)	8 (3.2)	31 (6.0)	63 (5.2)
Generalised allergic reaction**	20 (4.5)	19 (7.6)	22 (4.2)	61 (5.0)
Pyrexia	22 (5.0)	15 (6.0)	18 (3.5)	55 (4.5)
Vomiting	14 (3.2)	8 (3.2)	21 (4.0)	43 (3.5)
Malaise	10 (2.3)	7 (2.8)	11 (2.1)	28 (2.3)
Pain (not at injection site)	7 (1.6)	5 (2.0)	6 (1.2)	18 (1.5)
Pallor	7 (1.6)	2 (<1.0)	8 (1.5)	17 (1.4)
Lethargy	1 (<1.0)	8 (3.2)	7 (1.3)	16 (1.3)
Diarrhoea	6 (1.4)	3 (1.2)	6 (1.2)	15 (1.2)
Visual disturbance	4 (<1.0)	4 (1.6)	6 (1.2)	14 (1.2)
Coryza***	3 (<1.0)	8 (3.2)	3 (<1.0)	14 (1.2)
Paraesthesia	4 (<1.0)	5 (2.0)	4 (<1.0)	13 (1.1)
Dyspnoea	5 (1.1)	3 (1.2)	3 (<1.0)	12 (1.0)
Pruritus	3 (<1.0)	2 (<1.0)	7 (1.3)	12 (1.0)
Abdominal pain, upper	3 (<1.0)	1 (<1.0)	5 (1.0)	9 (<1.0)
Abdominal pain, not specified	2 (<1.0)	1 (<1.0)	6 (1.2)	9 (<1.0)
Cold sweat	4 (<1.0)	1 (<1.0)	3 (<1.0)	8 (<1.0)
Chills	2 (<1.0)	3 (1.2)	3 (<1.0)	8 (<1.0)
Myalgia	0 (0.0)	3 (1.2)	5 (1.0)	8 (<1.0)
Hyperhidrosis	2 (<1.0)	1 (<1.0)	2 (<1.0)	5 (<1.0)
Anaphylaxis	0 (0.0)	1 (<1.0)	0 (0.0)	1 (<1.0)
Other	49 (11.1)	35 (14.0)	50 (9.6)	134 (11.1)
Total	442	250	520	1212

includes syncopal seizures (36);

† includes 13 cases of pruritic rash

* pain (12), swelling (12), erythema or rash (11) and not specified (30)

** includes urticaria (27), hypersensitivity (8) and other generalised allergic reaction (26)

*** includes cough (4), rhinitis (5), sneezing (1), flu-like illness (2), nasopharyngitis (1), increased lacrimation (1)

Table C: Numbers of reported generalised allergic reaction adverse events following human papillomavirus vaccination, by reaction term, age and sex (1 January 2013 to 31 December 2013)

Reaction term	Males 12 to 13 years [n (%)]	Males 14 to 15 years [n (%)]	Females 12 to 13 years [n (%)]	Total
Urticaria	11 (40.7)	9 (33.3)	7 (25.9)	27
Hypersensitivity	3 (42.9)	2 (28.6)	2 (28.6)	7
Other generalised allergic reaction	5 (19.2)	8 (30.8)	13 (50.0)	26
Total	19 (31.7)	19 (31.7)	22 (36.7)	60

Table D: Numbers of reported syncope adverse events following human papillomavirus vaccination, by reaction term, age and sex (1 January 2013 to 31 December 2013)

Reaction term	Males 12 to 13 years [n (%)]	Males 14 to 15 years [n (%)]	Females 12 to 13 years [n (%)]	Total
Simple syncope	123 (44.2)	37 (13.3)	118 (42.4)	278
Syncopal seizure	17 (47.2)	4 (11.1)	15 (41.7)	36
Syncope with injury	6 (37.5)	2 (12.5)	8 (50.0)	16

Table E: Numbers of reported emergency department presentations or hospitalisations following human papillomavirus vaccination, by age and sex (1 January 2013 to 31 December 2013)

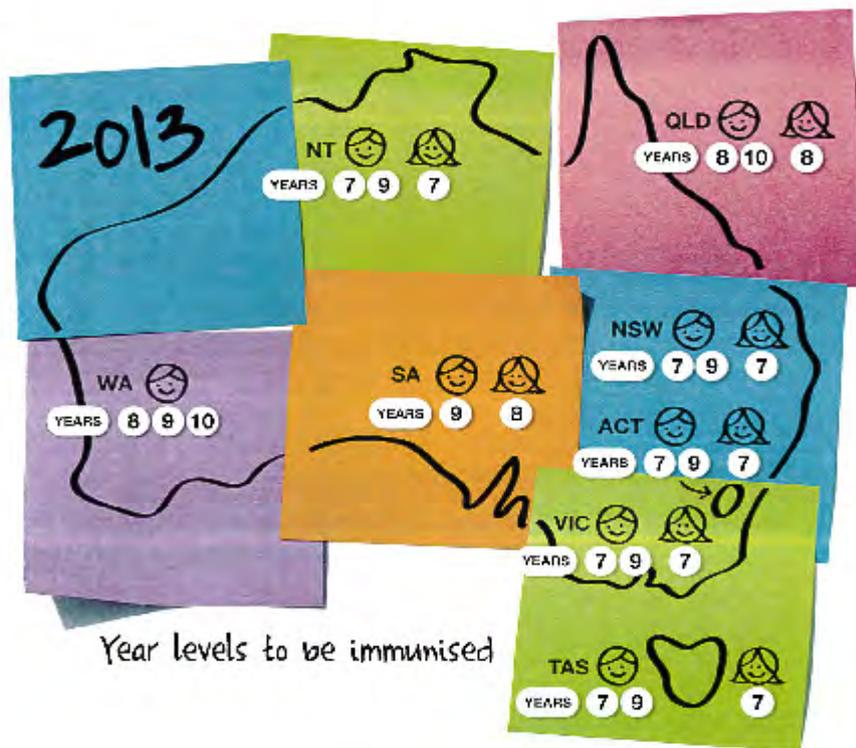
Reaction term	Males 12 to 13 years [n (%)]	Males 14 to 15 years [n (%)]	Females 12 to 13 years [n (%)]	Total
Emergency department presentation or hospitalisation	20 (51.3)	5 (12.8)	14 (35.9)	39

Annex D – Schedule for rollout of human papillomavirus vaccination school-based program



Program rollout by state/territory

Vaccinating against Human Papillomavirus (HPV) is the best way to prevent HPV-related cancers and disease. The HPV vaccine is being provided free in schools as part of the National Immunisation Program. Details on how the program will be rolled out in each state/territory are provided below.



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