Adverse events following HPV vaccination

11 years of surveillance in Australia

Phillips, Anastasia; Hickie, Megan; Totterdell, James; Brotherton, Julia; Dey, Aditi; Hill, Richard; Snelling, Tom; Macartney, Kristine

Published in:
Vaccine

DOI:
10.1016/j.vaccine.2020.06.039

Published: 27/08/2020

Document Version
Publisher's PDF, also known as Version of record

Vaccine 38 (2020) 6038–6046

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Adverse events following HPV vaccination: 11 years of surveillance in Australia

Anastasia Phillips [a,b,c,*], Megan Hickie [d], James Totterdell [c], Julia Brotherton [e,f], Aditi Dey [b,g], Richard Hill [d], Tom Snelling [c,h,i,j], Kristine Macartney [b,g]

[a] The University of Sydney, School of Public Health, Sydney, New South Wales 2006, Australia
[b] National Centre for Immunisation Research and Surveillance, Westmead, New South Wales 2145, Australia
[c] Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Nedlands, Western Australia 6009, Australia
[d] Therapeutic Goods Administration, Department of Health, Woden, Australian Capital Territory 2606, Australia
[e] Victorian Cytology Service Foundation, Carlton, Victoria 3053, Australia
[f] University of Melbourne, Parkville, Victoria 3010, Australia
[g] The University of Sydney, Discipline of Child and Adolescent Health, Sydney, New South Wales 2006, Australia
[h] Perth Children's Hospital, Nedlands, Western Australia 6009, Australia
[i] Curtin University, School of Public Health, Bentley, Western Australia 6102, Australia
[j] Menzies School of Health Research and Charles Darwin University, Darwin, Northern Territory, Australia

ARTICLE INFO

Article history:
Received 18 November 2019
Received in revised form 11 June 2020
Accepted 14 June 2020
Available online 22 July 2020

Keywords:
Human papillomavirus vaccine
Vaccination
Immunization
Vaccine safety
Adverse event
Syncope

ABSTRACT

Background: Australia was the first country to implement a fully funded vaccination program with quadrivalent human papillomavirus vaccine (4vHPV) in 2007, including males from 2013. We examined adverse events (AE) following vaccination with 4vHPV from 11 years of post-marketing data, focusing on a period of enhanced surveillance and adverse events of special interest (AESI).
Methods: AE following 4vHPV doses administered between April 2007 and December 2017 reported to Australia's national regulator, the Therapeutic Goods Administration, were examined; reports collected during enhanced surveillance in 2013 and 2014 were analyzed separately. Age and sex-specific rates, using denominator data from the national HPV vaccination register, were determined. Pre-specified AESI were identified using Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms and examined in detail.
Findings: Following nine million doses of 4vHPV vaccine administered in Australia, 4551 AE reports were identified. The crude reporting rate was 39.8 per 100 000 doses in the funded cohorts, excluding the enhanced surveillance period. The reported rate of syncope in 12 to 13-year-old males and females was 29.6 per 100 000 doses during enhanced surveillance and 7.1 per 100 000 doses during the remaining study period; rates of syncope were higher in younger compared to older adolescents. The rate of anaphylaxis (0.32 per 100 000 doses) was consistent with published rates. Other AESI including autoimmune disease, postural orthostatic tachycardia syndrome, primary ovarian insufficiency, Guillain-Barré syndrome, complex regional pain syndrome and venous thromboembolism, were reported at low rates and analysis did not reveal unexpected patterns that would suggest causal association.
Interpretation: AESI, apart from syncope, were reported rarely. The higher rate of syncope among younger adolescents highlights the need for management protocols to prevent syncope-related injury. Analysis of this large, longitudinal dataset in a country with high vaccine uptake, including a period of enhanced surveillance, affirms the safety profile of 4vHPV.

1. Introduction

Australia has a comprehensive, fully funded, national human papillomavirus (HPV) vaccination program with high coverage. A three-dose course of quadrivalent HPV vaccine (4vHPV) was introduced through the National Immunization Program (NIP) as a school-based program for 12 to 13-year-old females in 2007

* Corresponding author at: Sydney School of Public Health, The University of Sydney, Camperdown 2006, Australia.
E-mail address: aphi7007@uni.sydney.edu.au (A. Phillips).

https://doi.org/10.1016/j.vaccine.2020.06.039
0264-410X/

and males in 2013, with catch-up programs for other age groups [1].

HPV vaccination primarily aims to protect against cervical, anogenital and oropharyngeal cancers, and high-grade cervical lesions related to HPV infection [2]. Australia has been a world leader in demonstrating early program impacts, including declines in HPV prevalence, high grade cervical lesions and genital warts, as well as herd immunity effects, such as a decline in genital wart incidence in heterosexual males prior to the inclusion of males under the NIP [3]. Globally, HPV vaccine programs have been uniquely affected by concerns and issues related to vaccine safety that have negatively impacted upon vaccine uptake [4,5]. Although questions around safety have arisen in Australia, particularly in the early years of the program, relatively high uptake has been sustained with 80.2% three dose coverage among females and 75.9% among males in 2017, measured at 15 years of age [6].

HPV vaccine safety has been evaluated in pre-licensure clinical trials, post-marketing surveillance systems and observational studies worldwide [7,8]. While possible signals for an association of HPV vaccine with Guillain-Barré syndrome (GBS) [9,10] and venous thromboembolism (VTE) [11] were previously identified, these were excluded in subsequent observational studies [12–19]. Associations of HPV vaccine with other specific conditions and syndromes, including postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome (which overlaps with POTS), complex regional pain syndrome (CRPS) and primary ovarian insufficiency (POI) have been the subject of case reports and media interest [7]. While observational studies and expert reviews have not supported causal associations [20–24] these continue to be proposed. Only syncope has been consistently associated with HPV vaccination [25] and is known to be associated with vaccination more generally [26]. While generally benign and categorized as an immunization anxiety-related reaction [27] (rather than related to vaccine constituents), syncope following vaccination carries the risk of harm from syncope-related injury.

The initial safety concerns which arose following the introduction of the HPV vaccination program for females in Australia included a potential signal for anaphylaxis [28] and a series of reports of demyelinating syndromes [29]. In Australia, spontaneous reports of adverse events (AE) following vaccination are made to the national regulator of vaccines and other therapeutic goods, the Therapeutic Goods Administration (TGA). A Gardasil Expert Panel, established by the TGA, found that the incidence of demyelinating disorders following HPV vaccination was no higher than expected by chance, and that the rate of anaphylaxis was similar to that for other vaccines [30]. A high rate of syncope [31] was reported as an early concern but later found to be consistent with expected rates [32].

Following these evaluations, and as one of the first countries to implement a fully funded male program, a period of enhanced surveillance was implemented prospectively under the vaccine safety plan for introduction of the male program. Specifically, school-based AE surveillance was strengthened during 2013 and 2014 by: a) ensuring school immunization nurses recorded data on all AE occurring at the time of, or shortly after, vaccination (typically notified in the first four hours while immunization teams were still onsite at schools); b) a focus on collecting data on four pre-specified significant acute AEs: 1) anaphylaxis; 2) loss of consciousness (including syncope); 3) generalized allergic reaction and; 4) any condition requiring emergency department presentation or hospitalization [33]. During this period there was also more frequent analysis and reporting of data, intended to closely monitor safety in the new cohort (males) and compare it with females.

Safety surveillance data is now available for a large cohort of Australian adolescents over 11 years, including five years of data for males. Over this period, 4vHPV accounted for 99.9% of doses. We analyzed AE following 4vHPV doses administered between April 2007 and December 2017, focusing on determining age and sex-specific reporting rates, analyzing the impact of enhanced surveillance, and examining adverse events of special interest (AESI).

2. Methods

2.1. Study population and surveillance system characteristics

Australia has a population of approximately 25 million with over nine million doses of HPV vaccine administered between 2007 and 2017, according to the National HPV Vaccination Program Register (NHVPR). The HPV vaccine eligible population changed over the study period (Table 1). The majority of doses were given through the school-based vaccination program (94% for males, 69% for females overall and 92% for females once early community catch-up programs ceased).

Anyone can report a suspected AE to the TGA, including immunization providers, consumers, parents and pharmaceutical companies (Australian sponsors). In most jurisdictions (comprising eight states and territories) with responsibility for administering school-based vaccination programs, AE reporting is a statutory obligation for healthcare providers and predominantly occurs via state and territory vaccine safety surveillance mechanisms [34]. Reporters are requested to provide patient identifiers including date of birth or age, details of the product involved and the suspected adverse event, including dates. The reporter is also able to provide contact details, if consent is provided, to enable communication to seek additional information, if required. Reports are coded by the TGA on initial receipt based on the information provided in the report, using the internationally recognized Medical Dictionary for Regulatory Activities (MedDRA®) standardized terms, including Preferred Terms [35]. AE reports are stored within the TGA's Adverse Events Management Systems (AEMS) database.

Australian sponsors are required to apply seriousness coding to ensure legislated requirements are met. Other reports are coded (typically on initial receipt) as 'serious' based on criteria similar to the World Health Organization definition [27] and available information, where any of the following outcomes are documented: death; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability; life-threatening; or congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of these outcomes (a medically important event or reaction) may also be considered as serious. The TGA identifies and reviews medically important cases, which are flagged for review by a TGA medical officer. Where there is insufficient information for a serious AE report to be assessed, the TGA requests follow up information from the reporter with assistance from the relevant state or territory health department, including medical record information where required; however, this may not always be obtained.

We analyzed AEs within the TGA AEMS database following 4vHPV vaccine doses administered between 1 April 2007 and 31

Table 1
Nationally funded quadrivalent human papillomavirus (4vHPV) vaccination cohorts in Australia, 2007 to 2017.

Program delivery type	Age group	Year of program delivery
Primary program		
Female	12 to 13-years	2007 to 2017
Male	12 to 13-years	2013 to 2017
Catch-up program		
Female	14 to 26-years	2007 to 2009
Male	14 to 15-years	2013 to 2014

December 2017 for females, and between 1 February 2013 and 31 December 2017 for males, and reported by March 2018, to allow for reporting lag. Reports following nonavalent (9vHPV) or bivalent (2vHPV) HPV vaccine were excluded. The nonavalent vaccine was not available until 1 January 2018 after which it was added to the NIP, replacing 4vHPV vaccine. The bivalent vaccine was not supplied under the NIP and thus only administered to a small number of women within primary care over the study period; where no vaccine type was specified, reports were included and presumed to be 4vHPV. Reports following vaccination during pregnancy were identified using methods described previously [36].

For reports that were missing vaccination date, the date of reaction onset was used (the median lag time between vaccination date and reaction onset date was 0 days in this cohort). Where the reaction onset date was missing, the vaccination date was replaced with the date the report was received minus 15 days (the median lag time from vaccination to report in this cohort). Vaccination date was only used to determine annual rates and changes in rates over time. For description of individual AESI, additional free text data and medical record information, where available, was used to review time between vaccination and reaction onset. Where multiple 4vHPV doses were recorded within one report, the date of latest vaccination was used.

This study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (reference LNR/18/SCHN/440).

2.2. Descriptive analysis

AE reports were described for males and females by age group, reporter type, concomitant vaccination and seriousness code. We identified the top 10 most commonly reported MedDRA Preferred Terms by sex. Crude AE reporting rates per 100 000 doses administered were calculated across the entire program with age and sex-specific adverse event rates calculated for the NIP cohorts (Table 1). Rates for females and males in the primary target cohort were analyzed separately during the enhanced surveillance period. Doses administered by vaccine type, age, sex and time period were obtained from the NHVPR.

2.3. Adverse events of special interest (AESI)

AESI were determined by review of the literature [7,8,26] and from recent analyses of the United States (US) Vaccine Adverse Events Reporting System (VAERS) [37]. The following conditions were selected: syncope, venous thromboembolism (VTE), anaphylaxis, autoimmune disease (AID), postural orthostatic tachycardia syndrome (POTS), complex regional pain syndrome (CRPS) and Guillain-Barré syndrome (GBS). To allow comparison with international data, MedDRA Preferred Terms were selected as described previously in VAERS analyses [37] (Appendix 1) with the exception of GBS, where the term 'chronic inflammatory demyelinating polyradiculoneuropathy' (CIDP) was added (CIPD is considered a chronic form of GBS) [38]. These MedDRA terms were used as a sensitive search for potentially relevant cases, which were then further reviewed to determine whether cases met published criteria for the specific condition, where information was available. Case details were obtained from the TGA for all AESI except syncope. TGA case details included those obtained during investigation of the AE, which may include follow up information from the reporting source, medical record information and findings of any relevant expert panel. Reports of anaphylaxis, but not other AESI, were routinely classified according to Brighton Collaboration criteria by the TGA based on available data. [39] Reports were described by dose number where documented; there was no information on whether individuals received subsequent doses.

Signal detection methods were not applied in this retrospective analysis; signal detection is undertaken continuously and prospectively by the TGA using the provisional reporting ratio (PRR) and other methods.

3. Results

For 4vHPV doses given between 1 April 2007 and 31 December 2017, the TGA received 4556 adverse event reports up to 31 March 2018. Five reports for males were excluded from the main analysis (three for males vaccinated prior to the 2013 NIP expansion and two for male infants whose mothers were vaccinated) leaving 4551 adverse event reports.

Most reports were for the primary NIP funded cohort (12 to 13-year-old males and females) and the most common reporters were the respective state and territory health departments, reflecting established pathways for reporting to the TGA (Table 2). The most commonly reported MedDRA Preferred Terms were similar among males and females with headache and syncope the most common (Table 3).

Most reports (92.2%) were not coded as serious by the TGA (Table 2). Of the 354 that were coded as serious all were assessed by the TGA as meeting at least one criterion of the WHO definition for a serious AE; most (n = 224) were coded as serious due to the criterion 'caused or prolonged hospitalization'. The proportion of reports coded as serious changed over the study period with the highest proportion for females in 2009 (13.9%) and 2017 (13.2%) and the lowest proportion during the enhanced surveillance period (3.9% for females and 2.7% for males) (data not shown). The top 10 preferred terms were similar when limiting to reports coded as serious; injection site reaction was not one of the top 10 preferred terms for reports coded as serious.

3.1. Adverse event reporting rates in target cohorts

Between 1 April 2007 and 31 December 2017, almost 9.4 million doses of 4vHPV vaccine were recorded by the NHVPR in Australia, with an overall AE reporting rate of 48.5 per 100 000 doses administered across all age groups and 3.8 reports per 100 000 doses coded as serious.

One-hundred and two reports had either missing age, sex or both and were not included in age- and sex- specific AE rates. Vaccination date was missing in five per cent of cases (n = 243) and was substituted with reaction onset date for calculation of annual rates.

Excluding the enhanced surveillance period (2013–2014), the reporting rate among primary and catch-up NIP cohorts (Table 1) was 39.8 per 100 000 doses, compared to 72.3 during enhanced surveillance, where AE reporting rates were higher overall as compared with other time periods. During this enhanced surveillance period, the rate was notably lower among older males (14 to 15 years) compared to younger (12 to 13 years) males and females (39.1 compared to 88.4 per 100 000 doses) (Fig. 1, Appendix 2). Following the conclusion of enhanced surveillance, reporting rates for females 12 to 13 years of age were maintained at slightly higher levels than before 2013.

3.2. Pregnancy reports

Thirteen of the 4556 reports (including 3221 females and two reports for infant males), were identified as occurring during or following pregnancy. Four of the 13 reports identified spontaneous abortion and one was a report of preterm labor.

There were four reports of vaccination in pregnancy that specified AE as being various infant congenital anomalies. Three of these

Table 2
Summary of adverse event reports to the Australian Therapeutic Goods Administration (TGA) for males and females following quadrivalent human papillomavirus vaccine (4vHPV) given to females (2007 to 2017) and males (2013 to 2017).

	Female n (%)	Male n (%)	Unknown n (%)	Total n (%)
Total reports	3221 (70.8)	1298 (28.5)	32 (0.7)	4551
Coded as serious	295 (9.2)	54 (4.2)	5 (15.6)	354 (7.8)
4vHPV only	2167 (67.3)	604 (46.5)	22 (68.8)	2793 (61.4)
Reporter type				
Health Professional	447 (13.9)	53 (4.1)	6 (18.8)	506 (11.1)
Patient/Consumer	180 (5.6)	38 (2.9)	2 (6.2)	220 (4.8)
Sponsor	106 (3.3)	1 (0.1)	8 (25.0)	115 (2.5)
State/Territory surveillance system	2488 (77.2)	1206 (92.9)	16 (50.0)	3710 (81.5)
Age group (years)				
Under 12 years	99 (3.1)	39 (3.0)	3 (9.4)	141 (3.1)
12–13 years	1740 (54.0)	960 (74.0)	7 (21.9)	2707 (59.5)
14–17 years	695 (21.6)	277 (21.3)	5 (15.6)	977 (21.5)
18 years and over	627 (19.5)	9 (0.7)	4 (12.5)	640 (14.1)
Unknown	60 (1.9)	13 (1.0)	13 (40.6)	86 (1.9)

Table 3
Top 10 Preferred Terms and as a percentage of all MedDRA Preferred Terms for adverse events following quadrivalent human papillomavirus vaccine (4vHPV) reported to the Australian Therapeutic Goods Administration (TGA) for females (2007 to 2017) and males (2013 to 2017)[a].

Females	n (%)	Males	n (%)
Headache	550 (6.5)	Syncope	362 (13.8)
Syncope	467 (5.5)	Headache	188 (7.2)
Nausea	460 (5.5)	Pyrexia	156 (6.0)
Dizziness	423 (5.0)	Nausea	133 (5.1)
Pyrexia	324 (3.8)	Injection site reaction	120 (4.6)
Injection site reaction	307 (3.6)	Dizziness	111 (4.2)
Vomiting	262 (3.1)	Vomiting	108 (4.1)
Rash	255 (3.0)	Pre-syncope	85 (3.2)
Urticaria	212 (2.5)	Rash	64 (2.4)
Malaise	210 (2.5)	Urticaria	62 (2.4)

[a] Note that total number of Preferred Terms will not equal total number of AE reports as there may be more than one Preferred Term per report

reports involved individuals who did not yet know they were pregnant when they received the vaccine, and the fourth report did not contain enough narrative detail to determine this information. There was one report of eczema in an infant following administration of 4vHPV to the infant's mother during pregnancy. Other medical conditions were noted among data contained in these reports. No adverse outcomes were reported for the remaining pregnancy reports.

3.3. Adverse events of special interest (AESI)

Of pre-defined AESI, syncope (as a composite measured defined by the MedDRA Preferred Terms 'syncope', 'syncope vasovagal' or 'loss of consciousness' (see Appendix 1)) was the most commonly reported (Table 4). One death was reported with the cause stated as being cervical cancer years following HPV vaccination as an adult; the information provided in the report (which was based on a press article) was insufficient to determine causality.

3.3.1. Syncope

Of 856 AE classified as syncope, 825 were coded with the MedDRA Preferred Term 'syncope'; 23 were coded as 'loss of consciousness'; and eight were coded with both preferred terms. Preferred Terms that may relate to seizures ('seizure', 'partial seizures', 'generalized tonic-clonic seizure', 'clonic convulsion', 'tonic convulsion' and/or 'tonic clonic movements') were also assigned in a subset of reports coded with 'loss of consciousness' (n = 15) and a small proportion of reports coded as 'syncope' (n = 23). There were 14 reports coded with both 'syncope' and injury (including Preferred Terms 'concussion', 'contusion' and 'head injury') of which 13 were on the same day as vaccination.

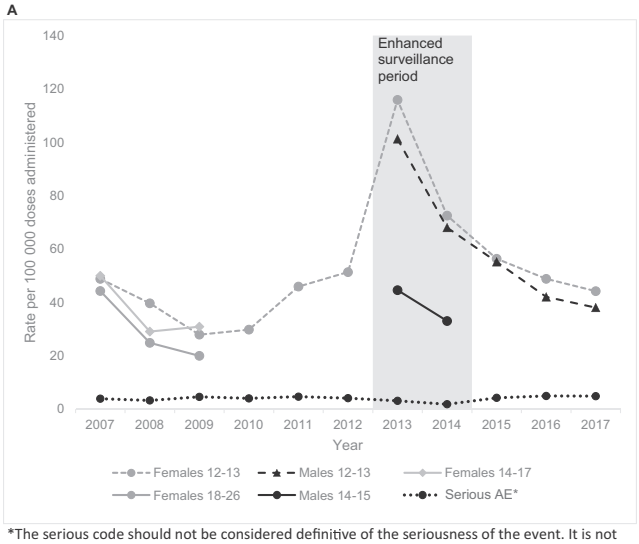

Fig. 1. Rates of adverse events following quadrivalent human papillomavirus vaccine (4vHPV) given to females (2007 to 2017) and males (2013 to 2017), reported by year; before, during and after an enhanced surveillance period (2013 to 2014). A: All adverse event reports including reports coded as serious based on preliminary review. B: Syncope (including MedDRA Preferred Terms 'syncope', 'syncope vasovagal' and 'loss of consciousness').

Table 4
Number and rate of potential adverse events of special interest (AESI) reported following quadrivalent human papillomavirus vaccine (4vHPV) in females (2007 to 2017) and males (2013 to 2017), in Australia.

AESI[a]	N[b]	Rate in overall surveillance period (enhanced surveillance period)[c]
Syncope	856	9.11 (23.8)
Anaphylaxis	30	0.32 (0.26)
Guillain-Barre syndrome	5	0.05
Postural orthostatic tachycardia syndrome	13	0.14
Autoimmune disease	13	0.14
Primary ovarian insufficiency	12	0.17[d]
Complex regional pain syndrome	4	0.04
Venous thromboembolism	3	0.03

[a] AESI were identified using grouped Preferred Terms as identified in Appendix 1
[b] Number of cases based on all those identified using prescribed search terms; not all cases are clinically confirmed, and causality is not assumed.
[c] Rate per 100 000 doses administered in overall surveillance period (2007–2017); rate during enhanced surveillance period (2013–2014) for AESI that are likely to occur on the day of vaccination (therefore responsive to enhanced surveillance methodology).
[d] Denominator includes female doses administered only (DA = 7,014,406).

Over half of syncope cases (n = 453) were reported during the enhanced surveillance period. During this period, the rate of reported syncope in the primary target cohort (12 to 13-year-old males and females) was 29.6 per 100 000 doses administered, over four fold higher than the rate during the remaining study period for this same age group (7.1 per 100 000 doses). The rate in 12 to 13-year-old males and females was around three times higher than the rate in 14 to 15-year-old males during the enhanced surveillance period (10.7 per 100 000 doses) (Fig. 1, Appendix 3). Rates decreased in 2014, following a peak in 2013 (from 47.1 to 13.9 per 100 000 doses in the primary target cohort). All reports followed dose 1, where dose number was documented (94.7%, n = 811).

3.3.2. Anaphylaxis

All 30 cases of anaphylaxis were coded using the MedDRA Preferred Term 'anaphylactic reaction' and all were confirmed by TGA coders to meet the Brighton Collaboration case definition. Of the 24 cases that had reaction onset date and vaccination date documented, all occurred on the day of vaccination; six reported concomitant administration of another vaccine (DTPa, Hepatitis B and/or influenza vaccines). The median age was 14 years; of the 28 cases where gender was reported, 26 were females.

Over one third of cases (n = 11) were reported in 2007. Low annual numbers were reported following 2007 (one to four cases per year), including during the enhanced surveillance period. The rate over the entire program was 0.32 per 100 000 doses administered and 0.26 per 100 000 doses during the enhanced surveillance period (Table 4). All reports followed dose 1, where dose number was documented (90%, n = 27).

3.3.3. Guillain-Barré syndrome (GBS)

Four cases were reported as GBS (three females and one male; median age 13 years) and one as CIDP. One of the four GBS cases was subsequently reclassified to CIDP. Three GBS cases were reported as confirmed based on nerve conduction studies; the fourth case, reviewed by the jurisdictional vaccine safety surveillance system, was determined to have met level 2 of diagnostic certainty using the Brighton Collaboration case definition. Two of the four GBS cases were reported to have had evidence of an antecedent illness (viral infection, mycoplasma infection) and one reported concomitant vaccination with DTPa vaccine.

3.3.4. Postural orthostatic tachycardia syndrome (POTS) and other postural dizziness

Of 13 cases identified using the MedDRA Preferred Terms 'postural orthostatic tachycardia syndrome', 'dizziness postural' or 'postural reflex impairment', most (n = 11) were in females. Six had been coded with the Preferred Term 'dizziness postural' of which five were self-limiting and occurred at the time of, or shortly after, vaccination; three had also received concomitant vaccination (hepatitis B, DTPa and/or influenza vaccine).

For the remaining seven cases coded with the MedDRA Preferred Term 'postural orthostatic tachycardia syndrome', all were reported from 2015 and there was insufficient information on symptoms, heart rate, blood pressure, investigations and/or duration of illness to establish a diagnosis of POTS according to published criteria [40]. Three cases were reported as being treated for orthostatic intolerance; two cases were reported to have also been diagnosed with chronic fatigue syndrome (CFS). Reaction onset dates were varied, but where documented, ranged from six months to over a year following vaccination.

3.3.5. Autoimmune disease (AID)

All 13 reports of AID were in females; the median age at vaccination was 15 years. Three had documented pre-existing AID and reported escalation in symptoms following 4vHPV vaccination. Of the remaining new onset cases, conditions reported included arthritis, systemic lupus erythematosus, dermatomyositis, autoimmune hemolytic anemia, ulcerative colitis, thyroiditis, diabetes mellitus, multiple sclerosis (coded with the preferred term 'autoimmune disorder'), and non-specific diagnoses. There was no pattern regarding time of onset following vaccination, which was reported in seven cases and varied from one week to three months. All reports followed dose 1, where dose number was documented (69%, n = 9).

3.3.6. Primary ovarian insufficiency (POI)

Of 12 reports identified using the MedDRA Preferred Terms 'premature menopause', 'ovarian disorder' and 'amenorrhea' (Appendix 1), three were published previously in an Australian case series [41]. Of the remaining cases, none had sufficient information to confirm a diagnosis and two had other generalized symptoms. Among the 12 cases, the median age at vaccination was 16 years; where documented, amenorrhea was reported to have occurred at variable times following vaccination.

3.3.7. Complex regional pain syndrome (CRPS)

The four reported cases of CRPS were all in females with a median age of 14 years and occurred in the individual's vaccinated arm. Three of the cases were also identified in a published case series and were reported to fulfill the diagnostic criteria for CRPS [42]. The remaining case had a history of injury to the hand prior to vaccination and was reported to have been diagnosed with CRPS by a pediatrician.

3.3.8. Venous thromboembolism (VTE)

The three reports of VTE were for deep vein thrombosis (DVT) in females with a median age of 19 years; two were documented to be taking the oral contraceptive pill and confirmed to have a thrombophilia. These DVTs were reported at variable times (five days to three months) following vaccination.

4. Discussion

This review of 11 years of post-marketing vaccine safety surveillance data from Australia's spontaneous adverse event reporting system has provided valuable information on HPV vaccine safety, as well as identified novel insights in relation to syncope during the two-year period of enhanced surveillance implemented when males were included in the vaccination program. While the overall adverse event reporting rate (48.5 per 100 000 doses administered) was slightly higher than the rate of reporting of AE following 4vHPV to the US VAERS (32.7 per 100 000 doses distributed) [37], this was impacted by higher reporting rates during the enhanced surveillance period. Excluding the enhanced surveillance period, the reporting rate (39.8 per 100 000 doses) among all funded primary and catch-up cohorts was similar to that of VAERS and is robust due to the use of denominator data obtained from the NHVPR on doses administered. In Australia in 2017, the number of 4vHPV AE reports in 7 to 17-year-olds (n = 277, 3 dose series) was similar to that recorded for other adolescent vaccines when taking into account scheduled doses (diphtheria-tetanus-pertussis containing vaccine [n = 173, single dose] and quadrivalent meningococcal vaccine [n = 83, single dose]), noting these vaccines are usually given concomitantly [43].

Reporting rates for 4vHPV were maintained at slightly higher levels following the enhanced surveillance period which likely reflects continued improvements in the reporting system and the commensurate increased awareness of and reporting of AE, as has been seen for other NIP vaccines over time [43]. While the increase in reporting during the enhanced surveillance period may suggest underreporting at other times, the higher proportion of reports that were non-serious during enhanced surveillance, as a result of instructions to nurses to report simple syncope, is reassuring.

Syncope was notable as the adverse event detected at an increased rate during the period of enhanced, nurse-led school-based surveillance. For the composite outcome of 'syncope' (including the MedDRA preferred terms 'syncope', 'syncope vasovagal' and 'loss of consciousness'), nearly half of all reported cases occurred during the two-year enhanced surveillance period, and the rate was over four times higher among both females and males in the primary target cohort during this time, as compared with the periods of routine surveillance. Inclusion of data from this enhanced surveillance period likely explains why the overall rate of syncope in this study was nearly double the rate reported by VAERS in 2018 using the same Preferred Terms [37].

Analysis of enhanced surveillance data also revealed that syncope was about three times as likely to occur in younger adolescents (aged 12 to 13 years) than in older males (14 to 15 years) as noted in a preliminary report by the TGA [33]. However, rates in 12 to 13 year old females were similar to that in males of the same age. Overall, this suggests an age-related relationship with this well-recognized immunization stress-related reaction, that has not previously been noted in population-level post marketing surveillance, to our knowledge.

This comprehensive data on syncope in both sexes of young adolescent vaccine recipients during the enhanced surveillance period allowed for a greater awareness of this condition among immunization program staff which ensured management protocols were in place to mitigate against syncope and prevent syncope-induced injury. The proportion of reports of syncope that were associated with a Preferred Term indicating injury was low in this study; similarly, the TGA review of the enhanced surveillance period identified very few syncopal episodes associated with injury or that had medical review, such that a decision was made not to request school-based reporting of simple syncopal events in the second year of enhanced surveillance [33]. Syncope following vaccination may be preventable but can create concern among vaccine recipients and/or carers and lead to negative perceptions of vaccination. It is important that immunization providers are aware of the frequency at which this can occur, particularly in younger adolescents, to avoid unduly negative outcomes [44].

The rate of anaphylaxis was higher in our study than the rate reported to VAERS (0.32 per 100 000 doses administered compared to 0.06 per 100 000 doses administered for VAERS) [37], but was similar to previously reported rates from Australia (0.32 per 100 000) [45], Canada (0.3 per 100 000) [46] and Europe (0.22 per 100 000) [47]. There was likely to be high awareness and reporting of anaphylaxis following initial signal investigation early in the HPV vaccination program in Australia. In this context, it was considered possible that there was a reduced threshold for using adrenaline and that syncope cases were more likely to meet the Brighton Collaboration criteria for anaphylaxis where anaphylaxis code was based on the treatment given. The reporting rate for anaphylaxis was not elevated during the enhanced surveillance period, during which it was a specified condition, further supporting our impression that anaphylaxis is rare after HPV vaccination, occurring in fewer than 1 in 300,000 young adolescent 4vHPV vaccine recipients.

We selected a number of other AESI to analyze in detail. Notably, while many reports were not confirmed to meet diagnostic criteria for the various conditions, reporting rates were nonetheless low, and comparable to rates using similar surveillance methods [37]. Spontaneous reporting systems like the AEMS have specific characteristics, including incomplete and selective reporting, that mean it is almost never possible to conclusively determine causality for an individual case based on available data. The absence of detailed clinical data, despite requests initiated by the TGA, made it difficult to assess a causal relationship to vaccination for the reports in this study. Importantly, these conditions occur at a background rate in the population, irrespective of vaccination, [48] although data on local and age-specific prevalence and incidence is often not available.

Only four cases of GBS, two of which had documented infection prior to disease onset, were reported during the entire 11-year surveillance period. The incidence of acute flaccid paralysis in Australia (of which GBS is the diagnosis in almost half of cases) has been estimated to be 0.8 per 100 000 children less than 15 years of age [49]. An early possible signal for GBS following HPV vaccine was identified and investigated in the United States [10] but was not confirmed in analyses of either VAERS [37] or the Vaccine Safety Datalink (VSD) [16,26]. While a cohort study in France suggested an elevated hazard ratio for GBS in vaccinated versus unvaccinated females [9], a UK self-controlled case series subsequently found no evidence of an increased risk in the 3 months following vaccination [12], and a Canadian study did not identify any increased risk of GBS-related hospitalization in HPV-target cohorts [14]. Evidence from our analysis is consistent with these studies in suggesting no increase in GBS in association with the introduction of HPV vaccination.

AE identified using search criteria that may suggest POTS (a syndrome of orthostatic intolerance associated with increase in heart rate in the absence of orthostatic hypotension and with light-headedness, palpitations and weakness [40]) were reported at a low rate in our study, similar to that from two analyses of US VAERS data (0.11 and 0.16 per 100 000 doses distributed, respectively) [37,50]. Although the prevalence of POTS in Australia is not well described, globally it is estimated to affect 0.2% of the population, supporting the observation of low rates in our cohort [40]. Many of the AE identified using our search strategy described simple postural dizziness on the day of vaccination; for

those reported as POTS specifically, it was not possible to establish a diagnosis of POTS according to published criteria in any case. Similarly, in a recent study based on VAERS data, only 29.5% (n = 29) of reports (using the preferred terms that we also used in our study) met POTS diagnostic criteria, and a pre-existing medical condition was documented in 20 cases, including five cases of CFS [50].

While some published reports have suggested an association between POTS and HPV vaccination [7], neither the World Health Organization's Global Advisory Committee on Vaccine Safety (GACVS) [51] nor the American Autonomic Society found evidence to support a causal association [52]. POTS is a heterogenous condition that is prevalent in the same population that receives HPV vaccine (adolescents and females) and symptoms can overlap with other syndromes that occur in adolescence, such as fatigue syndromes [52]; no association between HPV vaccination and increased risk of fatigue syndromes has been identified in epidemiological studies [20,22].

Most reports in our study were made after 2015 which may reflect the responsiveness of spontaneous reporting systems to media interest and public concern; clusters of non-specific symptoms attributed to POTS and CFS were reported in Denmark and increased following heightened media reporting in 2013 and 2015 [53]. Concern arising from causal attribution given to such temporal associations has led to declines in vaccine uptake in some countries [4,5], resulting in lost opportunities to prevent high grade cervical lesions [3], cervical and other cancers.

Of the other AESI examined, no vaccine safety signals were identified. Disease flare in individuals with pre-existing AID was reported in three cases; clinical trials did not identify any difference in the risk of disease flare between vaccinated and unvaccinated individuals with pre-existing AID [7]. New onset AID was reported rarely with no consistent pattern and variable syndromes reported; large, population-based studies have not demonstrated any increased risk of new-onset AID following 4vHPV [13,15]. The reported rate of POI was similarly low with lack of clinical and diagnostic data; a recent population-based epidemiological study found no significant risk of POI following 4vHPV (HR 0.30, 95% confidence interval 0.07 to 1.36) [24] and in 2017, the GACVS stated that there was no evidence for a causal association between HPV vaccine and POI [51]. The rate of complex regional pain syndrome was similar to that reported from the US (0.28 per million doses distributed) [37]. The rate of VTE in our study, based on just 3 cases, was comparable to the rate reported to VAERS [37]; recent evidence [15,17] has not supported any increased risk of VTE following the early safety signal identified in VAERS data [11].

While HPV vaccines are not recommended for use in pregnancy, data from spontaneous reporting systems as well as registries have not identified fetal loss or congenital anomalies above background rates or any concerning pattern of fetal loss following 4vHPV vaccine [7,36,54]; our study findings supports this conclusion. In 2017, the GACVS concluded that inadvertent administration of 4vHPV during pregnancy has not been shown to be associated with adverse outcomes [51].

A limitation of our study was interpretation of the seriousness code for reported AE which, while included for completeness, is primarily used as a guide for sponsor reporting. Although multiple attempts are made to obtain additional information from the reporter, coding may not be based on review of detailed and verified clinical data in every case and may not capture all medically important events [55]. These limitations should be considered in interpreting the code and it should not be considered definitive of the seriousness of the event. Identification of potential AESI was limited by the search terms selected, which may not have captured all potentially relevant cases. Review of individual AESI was limited by the case details obtained by the TGA during investigation; despite multiple attempts, sufficient detail is not always obtained. Our study is also subject to the inherent limitations of spontaneous reporting systems, including incomplete and selective reporting. While essential for signal detection and hypothesis generation (which is undertaken prospectively by the TGA and may lead to regulatory action), spontaneous reporting systems do not allow comparison to rates in unvaccinated populations; epidemiological studies are required to explore a potential association [56]. Comparison with AE rates for other adolescent vaccines, also delivered in schools under the NIP, was limited as vaccines are often given concomitantly with 4vHPV. The use of national vaccine registry data as a denominator for doses administered may slightly underestimate total doses due to under-notification from predominantly catch up vaccination delivered by primary care practices, which may have modestly inflated rate estimates.

5. Conclusion

Over an 11-year period, reporting rates of AE following 4vHPV administration in Australia were consistent with data from similar surveillance systems internationally and did not reveal any new or concerning safety issues. However, during a period of enhanced surveillance implemented to monitor introduction of the vaccine to adolescent males in addition to females, syncope was noted to occur at a higher rate in younger adolescents than previously observed. AESI, except for syncope, were reported rarely following 4vHPV and no new or concerning patterns were identified. This comprehensive analysis further contributes to the large body of existing data affirming the safe post-marketing profile of 4vHPV vaccine in both males and females and the value and characteristics of long-term spontaneous reporting systems in monitoring vaccine safety.

Funding source

PhD stipend funding (for AP) was provided by the National Health and Medical Research Council (NHMRC) and the Royal Australasian College of Physician (RACP). TS is supported by a Career Development Fellowship from the National Health and Medical Research Council (GNT1111657). The funding source had no role in the study design; collection, analysis and interpretation of data; writing of the report; or in the decision to submit the article for publication.

Author contributions

All authors attest they meet the ICMJE criteria for authorship. AP, KM, TS, JB and AD contributed to the conception and design of the study; AD, RH and MH contributed to acquisition of data; AP, JT, RH and MH analyzed the data; all authors contributed to interpretation of data; AP drafted the manuscript; all authors revised the manuscript critically for important intellectual content and approved the final version.

Declaration of Competing Interest

Over three years ago, JB was an investigator on two investigator-initiated HPV epidemiological studies that received partial unrestricted grants to support HPV typing components (cervical cancer typing study from Seqirus Australia, recurrent respiratory papillomatosis study from Merck) but has never received any personal financial benefits. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Han Wang from the National Centre for Immunisation Research and Surveillance along with Karen Winch and Karen Peasley from the National HPV Vaccination Program Register for assistance with provision of data. The NHVPR was fully funded by the Australian Department of Health and operated by VCS Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.06.039.

References

[1] Brotherton JM, Murray SL, Hall MA, Andrewartha LK, Banks CA, Meijer D, et al. Human papillomavirus vaccine coverage among female Australian adolescents: success of the school-based approach. Med J Aust 2013;199:614–7.
[2] Brotherton JML, Zuber PLF, Bloem PJN. Primary Prevention of HPV through Vaccination: Update on the Current Global Status. Curr Obstet Gynecol Rep 2016;5:210–24.
[3] Patel C, Brotherton JM, Pillsbury A, Jayasinghe S, Donovan B, Macartney K, et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent?. Euro Surveill 2018;23:1700737.
[4] Larson H. The world must accept that the HPV vaccine is safe. Nature 2015;528:9.
[5] World Health Organisation. Global Advisory Committee on Vaccine Safety, 5–6 June 2019. Wkly Epidemiol Rec 2019;28:306–16.
[6] National HPV Vaccination Program Register. Coverage Data. Victorian Cytology Service. <http://www.hpvregister.org.au/research/coverage-data>[Accessed: 14 September 2019].
[7] Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of Human Papillomavirus Vaccines: An Updated Review. Drug Saf 2018;41:329–46.
[8] Gee J, Weinbaum C, Sukumaran L, Markowitz LE. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. Hum Vaccin Immunother 2016;12:1406–17.
[9] Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France. Vaccine 2017;35:4761–8.
[10] Souayah N, Michas-Martin PA, Nasar A, Krivitskaya N, Yacoub HA, Khan H, et al. Guillain-Barre syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006–2009. Vaccine 2011;29:886–9.
[11] Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, et al. Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine. JAMA 2009;302:750–7.
[12] Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barre syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. Vaccine 2017;35:1729–32.
[13] Arnheim-Dahlstrom L, Pasternak B, Svanstrom H, Sparen P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013;347:f5906.
[14] Deceuninck G, Sauvageau C, Gilca V, Boulianne N, De Serres G. Absence of association between Guillain-Barre syndrome hospitalizations and HPV-vaccine. Expert Rev Vaccines 2018;17:99–102.
[15] Frisch M, Besson A, Clemmensen KKB, Valentiner-Branth P, Molbak K, Hviid A. Quadrivalent human papillomavirus vaccination in boys and risk of autoimmune diseases, neurological diseases and venous thromboembolism. Int J Epidemiol 2018;47:634–41.
[16] Gee J, Sukumaran L, Weintraub E. Risk of Guillain-Barre Syndrome following quadrivalent human papillomavirus vaccine in the Vaccine Safety Datalink. Vaccine 2017;35:5756–8.
[17] Naleway AL, Crane B, Smith N, Daley MF, Donahue J, Gee J, et al. Absence of venous thromboembolism risk following quadrivalent human papillomavirus vaccination, Vaccine Safety Datalink, 2008–2011. Vaccine 2016;34:167–71.
[18] Scheller NM, Pasternak B, Svanstrom H, Hviid A. Quadrivalent human papillomavirus vaccine and the risk of venous thromboembolism. JAMA 2014;312:187–8.
[19] Yih WK, Greene SK, Zichittella L, Kulldorff M, Baker MA, de Jong JL, et al. Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. Vaccine 2016;34:172–8.
[20] Donegan K, Beau-Lejdstrom R, King B, Seabroke S, Thomson A, Bryan P. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine 2013;31:4961–7.
[21] European Medicines Agency. Assessment Report: Review under Article 20 of Regulation (EC) No 726/2004, Human papillomavirus (HPV) vaccines. London: 2015. <http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500197129.pdf>.
[22] Feiring B, Laake I, Bakken IJ, Greve-Isdahl M, Wyller VB, Haberg SE, et al. HPV vaccination and risk of chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide register-based study from Norway. Vaccine 2017;35:4203–12.
[23] Global Advisory Committee on Vaccine safety. Statement on Safety of HPV vaccines. Geneva: World Health Organisation; 2015.
[24] Naleway AL, Mittendorf KF, Irving SA, Henninger ML, Crane B, Smith N, et al. Primary Ovarian Insufficiency and Adolescent Vaccination. Pediatrics 2018;142:e20180943.
[25] Committee to Review Adverse Effects of Vaccines Institute of Medicine. Adverse Effects of Vaccines: Evidence and Causality. Washington (DC): National Academies Press (US); 2011.
[26] Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011;29:8279–84.
[27] World Health Organisation. Global manual on surveillance of adverse events following immunisation. Geneva: World Health Organisation; 2016 <https://www.who.int/vaccine_safety/publications/aefi_surveillance/en/>.
[28] Brotherton JML, Gold MS, Kemp AS, McIntyre PB, Burgess MA, Campbell-Lloyd S, et al. Anaphylaxis following quadrivalent human papillomavirus vaccination. CMAJ 2008;179:525–33.
[29] Sutton I, Lahoria R, Tan I, Clouston P, Barnett M. CNS demyelination and quadrivalent HPV vaccination. Mult Scler 2009;15:116–9.
[30] Therapeutic Goods Administration. Gardasil (human papillomavirus vaccine). Australian Government Department of Health. <https://www.tga.gov.au/alert/gardasil-human-papillomavirus-vaccine>[Accessed: 14 September 2019].
[31] Buttery JP, Madin S, Crawford NW, Elia S, La Vincente S, Hanieh S, et al. Mass psychogenic response to human papillomavirus vaccination. Med J Aust 2008;189:261–2.
[32] Crawford NW, Clothier HJ, Elia S, Lazzaro T, Royle J, Buttery JP. Syncope and seizures following human papillomavirus vaccination: a retrospective case series. Med J Aust 2011;194:16–8.
[33] Therapeutic Goods Administration. Enhanced school-based surveillance of acute adverse events following immunisation with human papillomavirus vaccine in males and females, 2013. Canberra: Australian Government Department of Health; 2015.<https://www.tga.gov.au/enhanced-school-based-surveillance-acute-adverse-events-following-immunisation-human-papillomavirus-vaccine-males-and-females-2013>.
[34] National Centre for Immunisation Research and Surveillance. Vaccine Safety. NCIRS. <http://www.ncirs.org.au/health-professionals/vaccine-safety> [Accessed: 12 January 2020].
[35] Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999;20:109–17.
[36] Moro PL, Zheteyeva Y, Lewis P, Shi J, Yue X, Museru OI, et al. Safety of quadrivalent human papillomavirus vaccine (Gardasil) in pregnancy: adverse events among non-manufacturer reports in the Vaccine Adverse Event Reporting System, 2006–2013. Vaccine 2015;33:519–22.
[37] Arana JE, Harrington T, Cano M, Lewis P, Mba-Jonas A, Rongxia L, et al. Post-licensure safety monitoring of quadrivalent human papillomavirus vaccine in the Vaccine Adverse Event Reporting System (VAERS), 2009–2015. Vaccine 2018;36:1781–8.
[38] Odaka M, Yuki N, Hirata K. Patients with chronic inflammatory demyelinating polyneuropathy initially diagnosed as Guillain-Barre syndrome. J Neurol 2003;250:913–6.
[39] Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675–84.
[40] Sheldon RS, Grubb 2nd BP, Olshansky B, Shen WK, Calkins H, Brignole M, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm 2015;12:e41–63.
[41] Little DT, Ward HRG. Adolescent Premature Ovarian Insufficiency Following Human Papillomavirus Vaccination: A Case Series Seen in General Practice. J Investig Med High Impact Case Rep 2014;2. 2324709614556129-.
[42] Richards S, Chalkiadis G, Lakshman R, Buttery JP, Crawford NW. Complex regional pain syndrome following immunisation. Arch Dis Child 2012;97:913–5.
[43] Dey A, Wang H, Quinn H, Hiam R, Wood N, Beard F, et al. Surveillance of adverse events following immunisation in Australia annual report, 2017. Commun Dis Intell 2019;43.
[44] Kuntz JL, Firemark A, Schneider J, Henninger M, Bok K, Naleway A. Development of an Intervention to Reduce Pain and Prevent Syncope Related to Adolescent Vaccination. Perm J 2019;23:17–136.
[45] Cheng DR, Perrett KP, Choo S, Danchin M, Buttery JP, Crawford NW. Pediatric anaphylactic adverse events following immunization in Victoria, Australia from 2007 to 2013. Vaccine 2015;33:1602–7.
[46] Harris T, Williams DM, Fediurek J, Scott T, Deeks SL. Adverse events following immunization in Ontario's female school-based HPV program. Vaccine 2014;32:1061–6.
[47] Oberle D, Pavel J, Rieck T, Weichert S, Schroten H, Keller-Stanislawski B, et al. Anaphylaxis After Immunization of Children and Adolescents in Germany. Pediatr Infect Dis J 2016;35:535–41.
[48] Siegrist C-A. Autoimmune diseases after adolescent or adult immunization: what should we expect?. CMAJ 2007;177:1352–4.

[49] Morris AM, Elliott EJ, D'Souza RM, Antony J, Kennett M, Longbottom H. Acute flaccid paralysis in Australian children. J Paediatr Child Health 2003;39:22–6.
[50] Arana J, Mba-Jonas A, Jankosky C, Lewis P, Moro PL, Shimabukuro TT, et al. Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System. J Adolesc Health 2017;61:577–82.
[51] World Health Organisation. Meeting of the Global Advisory Committee on Vaccine Safety, 7–8 June 2017. Wkly Epidemiol Rec 2017;92:393–404.
[52] Barboi A, Gibbons CH, Axelrod F, Benarroch EE, Biaggioni I, Chapleau MW, et al. Human papillomavirus (HPV) vaccine and autonomic disorders: a position statement from the American Autonomic Society. Clin Auton Res 2019.
[53] Ward D, Thorsen NM, Frisch M, Valentiner-Branth P, Molbak K, Hviid AA, et al. to August 2017. Euro Surveill September 2009;2019:24.
[54] Goss MA, Lievano F, Buchanan KM, Seminack MM, Cunningham ML, Dana A. Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine. Vaccine 2015;33:3422–8.
[55] Dey A, Wang H, Quinn H, Pillsbury A, Glover C, Hickie M, et al. Surveillance of adverse events following immunisation in Australia annual report, 2018. Commun Dis Intell 2020;44.
[56] Tomianovic D, Bauwens J, Heininger U, Bonhoeffer J. Global Vaccine Safety Assessment: Challenges and Opportunities. Pediatr Infect Dis J 2016;35:446–8.