Syncope and seizures following human papillomavirus vaccination: a retrospective case series

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ABSTRACT

Objective: To quantify and characterise the reports of syncope and seizures following quadrivalent (4v) human papillomavirus (HPV) vaccination.

Design and setting: Retrospective case series of notifications to SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community), May 2007 – April 2009.

Main outcome measures: Incidence of syncope and seizure following 4vHPV vaccination; clinical outcomes.

Results: 97/1653 SAEFVIC reports met the study criteria: afebrile seizures (3), syncopal seizures (31) and syncope alone (63). Median age at vaccination was 15 years (range, 8–26 years). Injuries were reported in seven cases, including one vertebral fracture. A SAEFVIC clinic review was undertaken in 41% (40/97) and 22 patients received further 4vHPV vaccine doses administered supine, with no recurrences. The reporting rate after 4vHPV vaccine for syncope and syncopal seizures was 7.8/100 000 and 2.6/100 000 doses distributed, respectively.

Conclusion: Syncope and syncopal seizures occurred after 4vHPV vaccination in Victoria at rates similar to those seen internationally. Clinical review allowed clarification of the diagnosis and management, including safe administration of further doses under supervision.

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The link between human papillomavirus (HPV) infection and anogenital cancers is well established.[1] The quadrivalent HPV (4vHPV Gardasil [Merck/CSL]) vaccine protects against HPV (types 6, 11, 16, and 18) and is efficacious in preventing high-grade cervical lesions that could progress to cancer.[2] In Australia, approximately 700 women are diagnosed with cervical cancer each year, and there were 200 deaths in 2005.[3] A national HPV immunisation program was conducted between May 2007 and December 2009 for all females aged 12–26 years. The 2007 coverage rate in Victorian schools was 81% for the first dose, and 70% received all three doses.[4] The ongoing program includes Year 7 girls, aged 12–13 years.

Monitoring of adverse events following immunisation (AEFI) is important. AEFI temporally associated with vaccines are not necessarily causally related, but require further investigation. Clinical trials safety data demonstrated no difference in syncope between 4vHPV and control recipients (0.1% vaccine; 0.2% placebo) in more than 21 000 participants.[5] 4vHPV post-licensure safety monitoring, critical for less common AEFI, has been described internationally and in Australia.[6-8]

A syncopal episode (vasovagal, faint) occurs due to vagal nerve stimulation with bradycardia and transient hypotension. A painful stimulus (eg, vaccination) is a well described trigger.[9,10] Vaccinees appear pale and have a brief loss of or alteration in consciousness. The peak age for men and women is 15 years.[11,12] A brief seizure-like event can occur with syncope, secondary to transient hypoxia, with stiffening (tonic) movements and autonomic instability (eg, urinary incontinence). An individual with epilepsy may also have a seizure temporally associated with vaccination.

The 4vHPV vaccine implementation received high media coverage, including an episode of mass psychogenic illness occurring in Melbourne within weeks of commencement of the program.[13] In Valencia, Spain, two women were hospitalised after HPV vaccination, which led to temporary cessation of the local program in 2009.[14]

With a high level of international interest in AEFI after HPV vaccination, the aim of this study was to analyse detailed clinical information on SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community) cases of syncope and seizures after 4vHPV vaccination.

METHODS

SAEFVIC is the Victorian enhanced passive AEFI surveillance system established in April 2007.[15] Supplemental de-identified AEFI reports sent directly to the Therapeutic Goods Administration (TGA) were forwarded to SAEFVIC for assessment. AEFI reports are entered into a central database and clarified by an immunisation nurse with the consenting vaccinee, and/or reporter. Reports of significant AEFI are encouraged but not mandatory, and are predominantly received from immunisation nurses and general practitioners. SAEFVIC physician review appointments for children and adults are offered. Further 4vHPV vaccine doses are administered under supervision in-clinic, with patients lying supine 5 minutes before and 20 minutes after vaccination.

All AEFI reports to SAEFVIC from 1 May 2007 to 30 April 2009 were selected for analysis. AEFI with 4vHPV vaccine and coded as "syncope" or "seizure" were reviewed by a paediatrician (N W C), epidemiologist (H J C) and immunisation nurse (S E) for compliance with the *Australian immunisation handbook* definitions (Box 1).[16]

The 1.2 million distributed doses of 4vHPV vaccine (Helen Pitcher, Victorian Government Department of Health, personal communication) provided denominator data for the reporting rates. Descriptive analyses were conducted using Microsoft Excel (Microsoft Corporation, Redmond, Wash, USA).

RESULTS

In the 2-year study period, 29% (485/1653) of SAEFVIC reports included 4vHPV vaccine. A total of 192 reports involved seizures and/or syncope. Of these, 51% (97/192) of patients had received 4vHPV vaccine (Box 2). Nine reports were from the TGA (9%). All patients were female, and the median age was 15 years (range, 8–26 years).

Of the 94 syncopal episodes, 67% (63/94) had syncope alone, and 33% (31/94) had associated seizure activity, of which 23% (7/31) had urinary incontinence.

Three patients had afebrile seizures without syncope; all had a confirmed underlying epilepsy disorder. One patient had a generalised seizure 4 hours after the 4vHPV vaccine (dose 2). Another had an exacerbation

of complex partial seizures 4 hours after the 4vHPV vaccine (dose 2). Another patient experienced a generalised tonic–clonic seizure 2 days after receiving 4vHPV vaccine (dose 1). This resulted in a wedge fracture of spinal vertebrae (T5/T6), which was treated conservatively. A generalised epilepsy disorder was confirmed and anticonvulsant medication commenced.

AEFI according to 4vHPV vaccine dose number are detailed in Box 3. The 4vHPV vaccine was given alone in 85% (82/97) of reports, with concomitant vaccines including: hepatitis B (6); diphtheria-tetanus-acellular pertussis (6); varicella (1); and varicella and hepatitis B vaccine (2). After the AEFI, 11% (11/97) were taken to hospital by ambulance. An injury occurred in seven cases, none after syncope alone: head injury (5), mouth bleeding (1) and T5/T6 vertebral fracture (1).

SAEFVIC clinic review was undertaken in 41% (40/97) of cases, including 14 syncopal seizures. Of those not seen in-clinic, nine had already received three doses, 11 had insufficient demographic details recorded, and the remaining 37 had a telephone consultation with an immunisation nurse. Eight patients had an electrocardiogram (ECG), and all results were normal, including the QTc interval. Further 4vHPV vaccine doses were given to 22 clinic attendees: 14 with syncope, and eight with syncopal seizures, with no recurrences.

There were 1.2 million HPV vaccines distributed in Victoria over the study period. The overall reporting rate following 4vHPV was 7.8 per 100 000 doses distributed for syncope and 2.6 per 100 000 for syncopal seizures.

1 Adverse event following immunisation: definitions*

Syncopal episode (vasovagal, faint): episode of pallor and unresponsiveness or reduced responsiveness or feeling light-headed and occurring while vaccine being administered or shortly after (usually within 5 minutes), and bradycardia, and resolution of symptoms with change in position (supine position or head between knees or limbs elevated).

Seizure: witnessed sudden loss of consciousness and generalised, tonic, clonic, tonic–clonic, or atonic motor manifestations. Seizures can be:

- febrile — with fever ⩾ 38.5° C;
- afebrile — without fever; or
- syncopal — syncope/vasovagal episode followed by seizure(s).

* *Australian immunisation handbook*. 9th ed. 2008: 362.[16] ◆

DISCUSSION

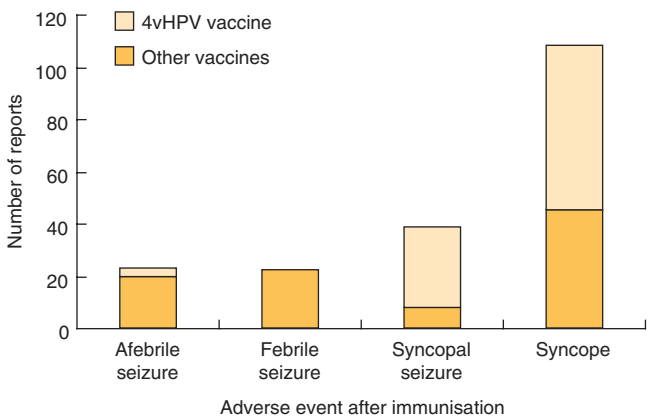
The Victorian reporting rate of syncope after 4vHPV vaccine of 7.8 per 100 000 doses distributed is similar to the United States Vaccine Adverse Event Reporting System (VAERS) reporting rate of 8.2 per 100 000.[6] As it is a passive AEFI surveillance system, it is likely to be an under-reported rate. It is, however, higher than the nationwide rate of syncope after 4vHPV vaccine of 2.5 per 100 000 doses distributed,[8] which may reflect the differing state-based AEFI reporting and clinical review systems within Australia. Syncopal episodes are not without potential morbidity and mortality, with one reported death following head injury after a syncope several minutes after immunisation.[17]

The reporting rate of syncopal seizures after 4vHPV vaccine found in our study was 2.6 per 100 000 doses distributed. This compares with 1.2 per 100 000 doses in the 1998 Australian measles catch-up vaccination campaign.[18] That campaign, however, included young children less likely to experience syncopal episodes. The 4vHPV vaccine post-licensure reporting of syncopal seizures has led the product information to include: "syncope, sometimes accompanied by tonic–clonic movements".[19]

The fact that syncope occurred after 4vHPV administration is not unexpected, as vaccination is a painful stimulus and a young female population was targeted in this catch-up program. Syncope has been reported to VAERS following the introduction of many vaccines targeted at adolescents, including quadrivalent meningococcal conjugate vaccine.[20] VAERS is a passive surveillance system, with reports made online from immunisation providers and parents. Although it is not linked to a clinical service, it can lead to review of case records and further investigation of potential flags raised through passive surveillance.

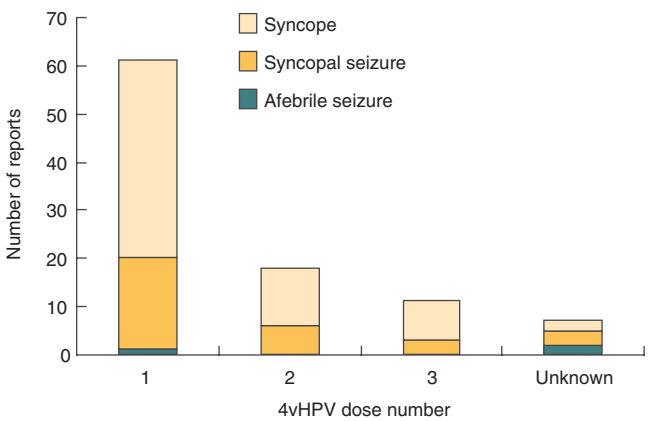
The differentiation between a syncopal seizure and an afebrile seizure is important and can be difficult. Of the 68 US AEFI reports of seizures after HPV vaccination, US researchers stated: "some reports to VAERS of seizures may be anoxic seizures resulting from syncopal episodes",[6] but they were unable to

2 Syncope and seizures after vaccination with quadrivalent human papillomavirus (4vHPV) vaccine and other vaccines*



*Reported to SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community), May 2007–April 2009. ◆

3 Syncope and seizures after vaccination with quadrivalent human papillomavirus (4vHPV) vaccine, by dose number*



*Reported to SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community), May 2007–April 2009. ◆

delineate this further. By obtaining further information from the reporter and vaccinee, SAEFVIC was able to better distinguish syncopal and afebrile seizures. Cardiogenic syncope (eg, prolonged QT syndrome) is an important differential if the patient has a history of palpitations or exertional syncope and/or a positive family history of sudden collapse or death.[12] Any flag on history or cardiac examination warrants further investigation (eg, ECG, cardiology review).

Limitations

SAEFVIC is a passive surveillance system, which will not have complete case ascertainment, and inherent limitations include reporting bias. Syncopal seizures may be more likely to be reported than syncope alone, due to the distress caused and concern regarding the diagnosis and possible recurrence with future vaccines. To determine the true incidence, an active surveillance system would need to be planned before introduction of a mass school immunisation program, as syncope cases may not present for medical attention.

TGA de-identified reports by medical practitioners (9%) often had missing demographic data, and clinical follow-up was not possible. Immunisation providers in Victoria are now encouraged to report AEFI directly to SAEFVIC. Another limitation is determining rates of AEFI with distributed rather than administered doses. When the national HPV register is fully operational, administered dose data will be available.[4]

Vaccine safety clinics operate in other Australian states, including New South Wales, South Australia and Western Australia. Integrating surveillance and clinical AEFI activities, through an enhanced passive surveillance model in all states and at a national level, could help improve assessment and coordinated review of AEFI in Australia.

Conclusion

This case series is a reminder to immunisation providers and other health professionals that syncope and syncopal seizures can occur following any painful stimulus, including vaccination. Monitoring for significant AEFI is a crucial part of post-licensure surveillance. Syncope and syncopal seizures occurred after 4vHPV vaccination in Victoria at reported rates similar to those seen internationally. SAEFVIC clinical review helped clarify the diagnosis and management of the AEFI.

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