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Quadrivalent HPV vaccination reactions

More hype than harm

Background

The quadrivalent human papillomavirus (HPV) vaccine Gardasil was licensed for use in June 2006. Since its approval more than 26 million doses of the vaccine have been distributed worldwide. There is ongoing debate as to the safety of the vaccine, with suggestions of a link between the vaccine and syncopal events, and the aetiology of more chronic conditions such as Guillain-Barre syndrome.

Objective

A case of subcutaneous emphysema secondary to quadrivalent HPV vaccination is described, and reported adverse events to quadrivalent HPV vaccination in both Australia and the United States are examined.

Discussion

On the basis of published peer reviewed literature, and from data analysis conducted by reputable agencies, the conclusion is drawn that adverse events are mild and self limiting and quadrivalent HPV vaccine is safe when administered according to the manufacturer's recommendations.

■ **A woman, 21 years of age, presented to a hospital emergency department complaining of a 'funny feeling' in the skin overlying the left deltoid muscle, approximately 2 hours after receiving a 0.5 mL intramuscular dose of quadrivalent human papillomavirus (HPV) vaccine (Gardasil). There were no other symptoms.**

Physical examination revealed her to be systemically well. There was a small punctum in the mid zone of the skin overlying the left deltoid muscle, with a surrounding zone of crepitus several millimetres in diameter. Neurovascular examination of the affected limb was unremarkable.

A diagnosis of iatrogenic subcutaneous emphysema (SCE) was made, and she was reassured and discharged. No treatment was prescribed. Recovery was uneventful with complete resolution over 3 days.

Discussion

Subcutaneous emphysema is a condition rarely seen in a hospital emergency department. It is usually observed as a consequence of the escape of gas from the tracheobronchial tree or gastrointestinal tract into the surrounding subcutaneous tissue. It may also occur secondarily to soft tissue infection by a gas producing micro-organism.

Iatrogenic SCE following the administration of hepatitis B vaccine has been reported in Spanish literature.¹ In this case, a 48 hour old neonate presented with irritability and food refusal. Physical and radiological examination demonstrated postvaccination SCE of the left lower limb, which resolved over 48 hours. The authors attributed the event to poor vaccination technique. Iatrogenic SCE has also been reported after dental procedures,^{2,3} laparoscopic surgery,⁴ and after epidural anaesthesia.⁵

The Gardasil licence application⁶ reported only one serious injection site adverse reaction from 11 778 vaccinated subjects. The subject complained of injection site pain with adjacent joint pain,

resulting in moderately decreased movement, lasting 5 months. There were no reports of vaccination mediated SCE.

In Australia, Gardasil is presented in two package forms: as a prefilled syringe and as an ampoule that requires an operator to draw the required volume of vaccine into a syringe. Although current Australian guidelines on best practice in immunisation technique state that small air bubbles do not need to be extruded through the needle before vaccination,⁷ it is surmised that the operator in the adverse event case failed to adequately expel a larger than usual volume of drawn up air from the syringe before vaccination.

Thus, it appears that the observed adverse event was not a result of the vaccine itself, but due to an error in injection technique.

Reported quadrivalent HPV vaccination adverse events

A search for information on quadrivalent HPV vaccination adverse events was conducted via PubMed and the search engine 'Google'. PubMed retrieved over 120 papers using the search term 'Gardasil', while over 1900 papers were found using the search stems 'papillo* adverse'. Only papers that provided reliable data and/or analysis of large cohorts were further examined – individual case studies were excluded as it was assumed that their information would have been incorporated into the larger data sets.

The 'Google' search provided approximately 83 800 'hits' to the search terms 'Gardasil adverse'. The web addresses of the top 20 hits were examined and the following information obtained:

- 14 of the 20 websites were 'private' websites (ie. sites belonging to nongovernment or privately funded organisations, or to private individuals or companies)
- four were websites of government agencies (eg. USA FDA)
- one was a web link of a large metropolitan Australian newspaper, and
- one was the website of an Australian professional medical organisation.

Of the 14 private websites, 12 could easily be determined to be 'against' the use of the quadrivalent HPV vaccine, and some have a record of opposition to the concept of vaccination, eg. Vaccine Information SA (VISA),⁸ and the National Vaccine Information Centre (NVIC), 'America's vaccine safety watchdog'.⁹

Reliable data on quadrivalent HPV vaccine adverse events retrieved from 'Google' replicated that which had been previously obtained from PubMed.

The best known of the quadrivalent HPV vaccination adverse reactions are those that have been widely reported by the popular Australian press, which appear to have been emotional and vasovagal type events among large groups of adolescents.^{10,11} These have been described by Clements¹² as a 'mass psychogenic illness', which has been defined as: 'the collective occurrence of a constellation of symptoms suggestive of organic illness but without an identified cause in a group of people with shared beliefs about the cause of the symptom(s)'.¹³

Similar events have been described following tetanus-diphtheria toxoid vaccination in Jordan,¹⁴ and oral cholera immunisation in

Vietnam.¹⁵ Although the USA Vaccine Adverse Event Reporting System (VAERS) – a national program of Centres for Disease Control and the Food and Drug Administration that monitors the safety of vaccines postlicensing – has reported an increased number of episodes of postvaccination syncope, primarily among females aged 11–18 years,¹⁶ recent publications have failed to reproduce these findings. Reeve et al¹⁷ in a rural north Queensland cohort reported only three significant adverse events from approximately 700 quadrivalent HPV vaccination episodes – these were all syncopal in nature, with immediate recovery. Brabin et al¹⁸ failed to detect a single serious adverse event from 3919 quadrivalent HPV vaccination episodes among 2817 English school girls aged 12–13 years.

The Australian experience

Up to 4 July 2008, 3.7 million doses of quadrivalent HPV vaccine had been distributed in Australia, with more than 26 million doses distributed worldwide. Up to 26 July 2008, 1013 suspected adverse events to quadrivalent HPV vaccine had been reported in Australia.¹⁹

Table 1 demonstrates that the vast majority of these adverse events were mild in nature and consistent with reactions reported for other vaccines. However, there are reports of more serious adverse events. There were 91 reports of urticarial rash and 12 cases of suspected anaphylaxis. Brotherton et al²⁰ examined these 12 cases in greater detail, and using the Brighton criteria²¹ determined that only eight of the 12 suspected cases were due to a true anaphylactic reaction, and that seven of the cases occurred in a New South Wales school based vaccination cohort. They concluded that the estimated rate of anaphylaxis following quadrivalent HPV (Gardasil) vaccination in the NSW school based cohort was 2.6 per 100 000 doses, significantly higher than in comparable school based delivery of other vaccines. However, the authors appear to have been selective in their use of available data – although seven of the eight confirmed cases of anaphylaxis after Gardasil vaccination were in the NSW school based cohort, they fail to analyse the entire data, which demonstrated only eight confirmed cases of anaphylaxis in the entire nation. Once this is taken into account, the observed rate of anaphylaxis to the quadrivalent HPV vaccine in Australia falls

Table 1. Frequent mild adverse events reported after Gardasil vaccination in Australia to 26 July 2008¹⁹

Adverse event	No. reported (n=1013)	% of total adverse events
Injection site reaction (soreness/swelling/redness)	203	20
Headache	202	20
Dizziness	156	15
Nausea	164	16
Vomiting	70	7
Total	795	78

to approximately 0.2 cases per 100 000 doses, which compares favourably to other vaccines administered to children and adolescents which have reported anaphylaxis rates of 0–3.5 cases per million vaccine doses.²²

The USA experience

Up to 30 April 2008, over 12 million doses of quadrivalent HPV vaccine had been distributed in the USA, and 7802 reports of adverse events received by the VAERS program.²³ Similar to the Australian experience, the most common adverse event has been (brief) soreness at the site of injection. The VAERS program defines a serious adverse event as one which involves death, hospitalisation, permanent disability or a life threatening illness. Less than 7% of adverse events reported to VAERS have been classified as serious; approximately half the average report rate for vaccines overall.

There have been 15 deaths reported following quadrivalent HPV vaccination, of which 10 reports provided sufficient information to allow further analysis – none of the examined cases established a causal relationship between the vaccination and death. In prelicensing testing, 10 quadrivalent HPV vaccine recipients and seven placebo recipients died during the trial period – none of the deaths among the vaccine recipient group were considered to be related to the vaccine.

An area of intense concern in the USA experience has been the relationship between quadrivalent HPV vaccine and Guillain-Barre syndrome (GBS). The VAERS have received 31 reports of GBS after quadrivalent HPV vaccination. Of these:

- 10 were confirmed cases; five had received concurrent vaccination with quadrivalent meningococcal conjugate vaccine (MCV4) (Menacta), which has been demonstrated to precipitate GBS
- nine cases are undergoing further evaluation
- seven cases failed to meet the case definition for GBS
- four cases were unconfirmed reports, and
- one case had symptoms of GBS before vaccination.

Epidemiological evaluation of the incidence of GBS among those aged 9–26 years suggest that the reports of GBS received by VAERS are within the range that could be expected to occur by chance alone after any vaccination.

Conclusion

Quadrivalent HPV vaccine adverse events are generally mild and self limiting, although there are reports of more serious adverse events of which urticarial rash and anaphylactic reaction to the vaccine (or its constituents) has been established. Further evaluation of quadrivalent HPV vaccine is required to determine the role, if any, of the vaccine in the aetiology of other disorders such as GBS.

Although the differentiation of HPV vaccine caused adverse events from events observed only by chance may be difficult, on the basis of information published in the peer reviewed literature and from data analysed by reputable agencies, the quadrivalent HPV vaccine appears to be safe when administered according to the manufacturer's recommendations.

Conflict of interest: none declared.

Acknowledgment

The author wishes to thank Dr Tonia Mezzini for her assistance with the preparation of this manuscript.

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