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RESEARCH

Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: retrospective cohort study

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ABSTRACT

Objective To describe the outcomes of clinical evaluation, skin testing, and vaccine challenge in adolescent schoolgirls with suspected hypersensitivity to the quadrivalent human papillomavirus vaccine introduced in Australian schools in 2007.

Design Retrospective cohort study.

Setting Two tertiary paediatric allergy centres in Victoria and South Australia, Australia.

Participants 35 schoolgirls aged 12 to 18.9 years with suspected hypersensitivity reactions to the quadrivalent human papillomavirus vaccine.

Main outcome measures Clinical review and skin prick and intradermal testing with the quadrivalent vaccine and subsequent challenge with the vaccine.

Results 35 schoolgirls with suspected hypersensitivity to the quadrivalent human papillomavirus vaccine were notified to the specialised immunisation services in 2007, after more than 380 000 doses had been administered in schools. Of these 35 schoolgirls, 25 agreed to further evaluation. Twenty three (92%) experienced reactions after the first dose. Thirteen (52%) experienced urticaria or angio-oedema, and of these, two experienced anaphylaxis. Thirteen had generalised rash, one with angio-oedema. The median time to reaction was 90 minutes. Nineteen (76%) underwent skin testing with the quadrivalent vaccine: all were skin prick test negative and one was intradermal test positive. Eighteen (72%) were subsequently challenged with the quadrivalent vaccine and three (12%) elected to receive the bivalent vaccine. Seventeen tolerated the challenge and one reported limited urticaria four hours after the vaccine had been administered. Only three of the 25 schoolgirls were found to have probable hypersensitivity to the quadrivalent vaccine.

Conclusion True hypersensitivity to the quadrivalent human papillomavirus vaccine in Australian schoolgirls was uncommon and most tolerated subsequent doses.

INTRODUCTION

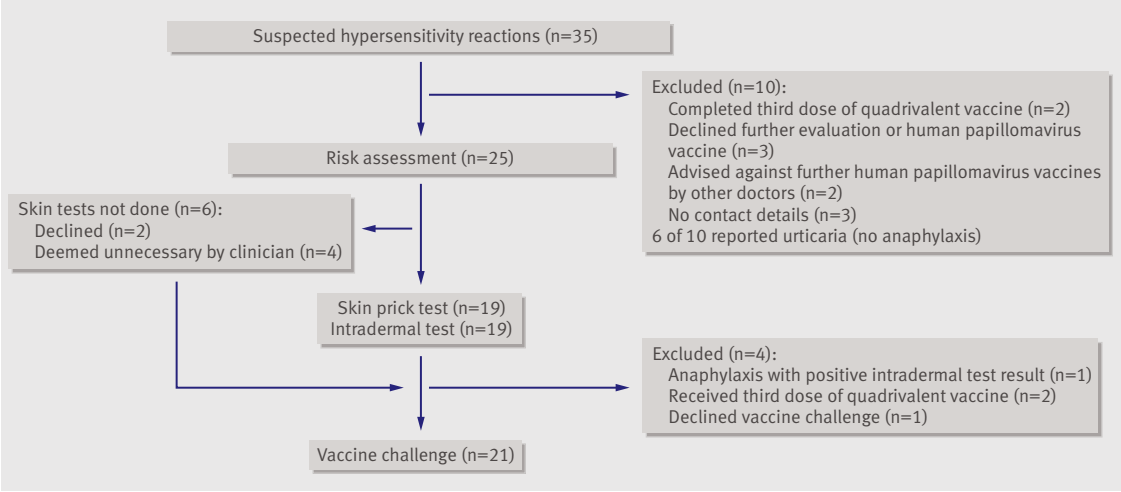
A quadrivalent human papillomavirus vaccine (Gardasil; Merck, NJ, USA) was included in the Australian national immunisation programme in April 2007 for females aged 12-26 years. Adolescent schoolgirls received the vaccine in a secondary school vaccination programme and reports of vaccine related adverse events soon followed.[1] Constituents of the quadrivalent vaccine, such as aluminium salts,[2 3] polysorbate 80,[4] and yeast,[5] have been associated with hypersensitivity reactions. The vaccine also shares constituents with other vaccines, such as hepatitis B (H-B-Vax II; Merck, NJ, USA) and diphtheria, tetanus, and pertussis (Boostrix; GlaxoSmithKline, Rixensart, Belgium), which are given to Australian adolescents at age 13 and 15 years, respectively. A bivalent human papillomavirus vaccine (Cervarix; GlaxoSmithKline, Rixensart, Belgium) lacks these constituents and may be an alternative for patients with hypersensitivity to the quadrivalent vaccine (table 1).

We describe the outcomes of clinical evaluation, skin testing, and vaccine challenge in Australian adolescent schoolgirls with suspected hypersensitivity to the quadrivalent human papillomavirus vaccine.

METHODS

In the Australian states of Victoria and South Australia, specialised immunisation services are notified of reported vaccine related adverse events. Adolescent schoolgirls with suspected hypersensitivity reactions to the quadrivalent human papillomavirus vaccine, including urticaria, generalised rash, angio-oedema, or anaphylaxis, were referred to tertiary paediatric allergy centres for further evaluation and are included in this retrospective cohort study. We include only girls who received the vaccine in school and not those who may have received the vaccine elsewhere. A detailed history of the reaction was obtained, including previous doses of the quadrivalent vaccine, concomitant vaccines, and time and severity of reaction. We also recorded any history of atopic disease, recurrent urticaria, or drug or vaccine related adverse reactions.

Skin prick and intradermal tests were carried out with 1:10 dilutions of both the quadrivalent and the bivalent human papillomavirus vaccines and 100 mg/ml



Flow chart of clinical evaluation through trial

polysorbate 80 (Tween 80; Merck, Darmstadt, Germany).[6] We used histamine and normal saline as positive and negative controls. Additional skin prick tests to other potential allergens were done as guided by clinical history. We measured skin wheals 15 and 20 minutes after skin prick and intradermal testing, respectively, and considered diameters of 3 mm or more above the saline control as a positive result.

Vaccine challenges were administered intramuscularly under medical supervision. All the girls were offered challenge with the quadrivalent vaccine unless there was previous anaphylaxis or a positive skin test result to the vaccine. A 0.1 ml dose was followed 30 minutes later by a 0.4 ml dose. The bivalent vaccine (0.5 ml) was given if requested by the recipient. We followed up the schoolgirls by telephone one week after vaccination and recorded any adverse events. Further vaccinations were planned for those who tolerated the challenge, to complete the three dose schedule.

RESULTS

Thirty five schoolgirls with suspected hypersensitivity to the quadrivalent vaccine were reported in 2007, after more than 380 000 vaccine doses had been administered in schools in Victoria and South Australia. Twenty five of these schoolgirls (71%) agreed to undergo further evaluation and were reviewed between August 2007 and February 2008, at a median of 5.7 months (range 1.6-9.9 months) after the reaction (figure). The age of the schoolgirls, proportion with reactions to the first dose, and proportion with urticaria reactions were similar in those excluded and those evaluated. No cases of angio-oedema or anaphylaxis occurred in the excluded group (six in the evaluated group) and time to reaction was significantly longer (median 24 hours) and positively skewed than in the evaluated group.

The median time to reaction after vaccination in the evaluated group was 90 minutes. Thirteen of the 25 evaluated schoolgirls experienced urticaria or angio-oedema, and of these, two experienced anaphylaxis (table 2). Thirteen experienced generalised rash, one with angio-oedema.

Nineteen (76%) of the 25 evaluated schoolgirls received only the quadrivalent vaccine, whereas six had concomitant vaccines (table 2). Twenty three of the 25 (92%) reported reactions after the first dose of

Table 1 | Examples of constituents of vaccines

Variables	Vaccine (manufacturer)			
	H-B-Vax II (Merck)	Boostrix (GlaxoSmithKline)	Gardasil (Merck)	Cervarix (GlaxoSmithKline)
Microorganism	Double stranded DNA hepatitis virus family *Hepadnaviridae*	Bordetella pertussis, Corynebacterium diphtheriae, Clostridium tetani	Recombinant human papillomavirus proteins, virus-like particles 6, 11, 16, and 18	Recombinant human papillomavirus proteins, virus-like particles 16 and 18
Medium	Saccharomyces cerevisiae	Stainer-Scholte liquid; Fenton medium; Lantham medium	Saccharomyces cerevisiae	Baculovirus or Trichoplusnia
Preservative	None	Polysorbate 80 ≤100 µg; formaldehyde	Polysorbate 80 50 µg; L-histidine	None
Adjuvant	Aluminium hydroxyphosphate sulphate; potassium salt	Aluminium hydroxide; sodium chloride	Aluminium hydroxyphosphate sulphate; sodium chloride; sodium borate	Aluminium hydroxide and monophosphoryl lipid A; sodium chloride; sodium phosphate monobasic
Current immunisation schedule in Australia	Infant schedule; catch-up schedule 11-15 years	15-17 years	School years 7, 10, 11, and 12 until 26 years (registered for 9-26 year olds)	(registered for 10-45 years)

quadrivalent vaccine. Four of the 25 reported reactions after the second dose, and of these, three reported reactions after the first and the second doses. One patient reported a reaction after the third dose.

Fifteen (60%) of the 25 evaluated schoolgirls had a history of current atopic disease: allergic rhinitis in 12 (48%), asthma in eight (32%), atopic dermatitis in five (20%), allergic conjunctivitis in five (20%), and food allergy in three (12%). Two girls had recurrent urticaria and none had a history of hypersensitivity to yeast, drugs, or vaccines. Food, environmental allergens, and drug allergens that may have been associated with the

Table 2 | **Details of 25 girls reporting adverse reactions to the quadrivalent human papillomavirus vaccine**

Vaccine category, dose, and concomitant vaccines	Suspected hypersensitivity reaction	Onset of reaction (min)	Skin prick test result	Intradermal test result	Vaccine challenge	Challenge reaction	Notes
Probable hypersensitivity (median 17.5 minutes):							
Third dose	Urticaria, angio-oedema, laryngeal oedema, tachypnoea, palpitations	390	Negative	Negative	NA	NA	Anaphylaxis after third dose
First (and second) dose	Urticaria (urticaria, angio-oedema, hoarse voice, laryngeal oedema)	20 (15)	Negative	Positive	NA	NA	Anaphylaxis after second dose
First dose	Urticaria	15	Negative	Negative	Quadrivalent HPV vaccine	Reported limited urticaria four hours later	
Possible hypersensitivity (median 16 hours):							
Second dose	Urticaria	960	Negative	Negative	Elected not to proceed with challenge before evaluation	Elected not to proceed with challenge before evaluation	Hyperventilating after intradermal test. Reported non-specific limited rash several hours after intradermal test
Unlikely hypersensitivity (median 19 hours):							
First dose plus H-B-Vax II	Generalised rash, angio-oedema	2	Negative	Negative	Bivalent HPV vaccine	None	Hypersensitivity unlikely as did not receive quadrivalent vaccine
First dose plus H-B-Vax II	Generalised rash	120	Negative	Negative	Bivalent HPV vaccine	None	Hypersensitivity unlikely as did not receive quadrivalent vaccine
First dose	Generalised rash	2160	Negative	Negative	Quadrivalent HPV vaccine	Reported nausea, vomiting, and lethargy two days later	Hypersensitivity unlikely as reaction was different to previous reaction
First dose plus H-B-Vax II	Urticaria, angio-oedema	2880	Negative	Negative	Bivalent HPV vaccine	None	Hypersensitivity unlikely as did not receive quadrivalent vaccine
Not hypersensitivity (median 90 minutes):							
First dose plus Varilrix plus tetanus	Generalised rash	1440	Negative	Negative	Quadrivalent HPV vaccine	None	
First dose plus H-B-Vax II	Generalised rash (eczema)	1440	NA	NA	Quadrivalent HPV vaccine	None	Skin testing deemed unnecessary
First dose	Generalised rash	1080	NA	NA	Quadrivalent HPV vaccine	None	Skin testing deemed unnecessary
First dose	Generalised rash	1080	NA	NA	Quadrivalent HPV vaccine	None	Declined skin testing
First dose	Generalised rash	180	Negative	Negative	Quadrivalent HPV vaccine	None	
First dose plus Boostrix	Generalised rash	720	Negative	Negative	Quadrivalent HPV vaccine	None	
First dose	Urticaria	2880	Negative	Negative	Quadrivalent HPV vaccine	None	
First dose	Angio-oedema	5	Negative	Negative	Quadrivalent HPV vaccine	None	
First dose	Generalised rash	90	Negative	Negative	Quadrivalent HPV vaccine	None	
First dose	Generalised rash	1440	NA	NA	Quadrivalent HPV vaccine	None	Declined skin testing
First dose	Angio-oedema	1440	Negative	Negative	Quadrivalent HPV vaccine	None	
First dose	Urticaria	15	Negative	Negative	Quadrivalent HPV vaccine	None	
First (and second) dose	Urticaria (urticaria)	30 (20)	Negative	Negative	Quadrivalent HPV vaccine	None	Twin of schoolgirl
Third dose	Urticaria	10	Negative	Negative	NA	NA	Twin of schoolgirl
First dose	Generalised rash, tachypnoea	20	Negative	Negative	Quadrivalent HPV vaccine	None	Thought to hyperventilate after first dose
First dose	Generalised rash	30	Negative	Negative	Quadrivalent HPV vaccine	None	
First (and second) dose	Urticaria (urticaria)	10 (10)	Negative	Negative	Quadrivalent HPV vaccine	None	

HPV=human papillomavirus; NA=not applicable; H-B-Vax II=vaccine against hepatitis B (Merck); Varilix=vaccine against varicella (GlaxoSmithKline); Boostrix=vaccine against diphtheria, tetanus, and pertussis (GlaxoSmithKline).

vaccine related adverse event were excluded by a detailed history taking and, if clinically indicated, skin prick tests.

Nineteen of the 25 evaluated schoolgirls (76%) underwent skin prick testing to the quadrivalent vaccine, polysorbate 80, and bivalent vaccine. All the results were negative. The 19 schoolgirls underwent intradermal testing, of which one (table 2) had a positive result to the quadrivalent vaccine and negative results to polysorbate 80 and the bivalent vaccine. One schoolgirl experienced hyperventilation during intradermal testing (table 2) and reported a limited nonspecific rash several hours later. She declined further vaccination against human papillomavirus.

Challenge with the quadrivalent vaccine was carried out in 18 (72%) of the 25 evaluated schoolgirls. Three of the seven schoolgirls who were not challenged with the quadrivalent vaccine elected to receive the bivalent vaccine as they had concerns about the quadrivalent vaccine despite a negative skin test result. Vaccine challenges were not done in the two schoolgirls who had completed the three doses of the schedule or the one girl who declined further vaccination, and challenge was contraindicated in one girl who had anaphylaxis and a positive skin test result to the quadrivalent vaccine.

Seventeen of the 18 schoolgirls challenged with the quadrivalent vaccine and all three challenged with the bivalent vaccine remained well one week after vaccination. One schoolgirl reported limited urticaria over the limbs and trunk four hours after challenge with the quadrivalent vaccine (table 2). Supervised challenge with the bivalent vaccine for her third dose of human papillomavirus vaccine was well tolerated.

The 25 evaluated schoolgirls were classified into one of four categories (table 2): probable hypersensitivity—those with anaphylaxis, a positive skin test result for the quadrivalent vaccine, or reproducible reactions to challenge with the quadrivalent vaccine; possible hypersensitivity—those with reactions to skin testing who were not challenged with the quadrivalent vaccine; unlikely hypersensitivity—those with negative skin test results to the quadrivalent vaccine who were not challenged with the quadrivalent vaccine, or were challenged with the quadrivalent vaccine but did not experience a reproducible reaction; and not hypersensitivity—those with negative skin test results for the quadrivalent vaccine and no adverse reaction to subsequent challenge with the quadrivalent vaccine.

Schoolgirls in the probable hypersensitivity group were more likely to present with urticaria than those in the unlikely hypersensitivity group (likelihood ratio 9.0) and not hypersensitivity group (10.2), and had a median time to reaction of 17.5 minutes compared with 19 hours in the unlikely hypersensitivity group and 90 minutes in the not hypersensitivity group (table 2). Other clinical features, including number of doses of the quadrivalent vaccine, concomitant vaccines, recurrence of reactions to the quadrivalent vaccine, and current atopic disease or recurrent urticaria, did not predict hypersensitivity to the quadrivalent vaccine.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hypersensitivity reactions to vaccines are uncommon

WHAT THIS STUDY ADDS

True hypersensitivity to the quadrivalent human papillomavirus vaccine is uncommon and most females tolerate subsequent doses

DISCUSSION

We evaluated suspected hypersensitivity in adolescent females immunised with a human papillomavirus vaccine in Australian schools. Only three of the 25 evaluated schoolgirls had probable hypersensitivity to the quadrivalent human papillomavirus vaccine after 380 000 doses had been administered in schools. Seventeen of the 18 girls subsequently challenged with the quadrivalent vaccine tolerated revaccination. Our data suggest that true hypersensitivity to the quadrivalent vaccine is uncommon and that suspected hypersensitivity reactions such as urticaria are often idiosyncratic and not usually a contraindication to further vaccinations. Studies of other vaccines have found that most reactions after immunisation are not due to hypersensitivity and revaccination is usually well tolerated.[7-9]

Although we excluded 10 of 35 schoolgirls with suspected hypersensitivity to the quadrivalent vaccine from our evaluation, reactions in the excluded group were mostly mild and delayed in presentation, suggesting that we did not miss any important cases of suspected hypersensitivity to the quadrivalent vaccine. All reported cases of anaphylaxis were evaluated.

Time to anaphylaxis was 15 minutes in one girl and 6.5 hours in another. As anaphylaxis after childhood vaccinations usually occurs within one hour,[10 11] 6.5 hours is beyond any standard observation period after immunisation. Consistent with the delayed presentation, one of the girls had no evidence of IgE mediated hypersensitivity to the quadrivalent vaccine and we postulate her reaction was mediated by IgG or complement, or both. As she was not rechallenged with the quadrivalent vaccine, however, hypersensitivity was not confirmed.

One of the girls had a positive intradermal test result to the quadrivalent vaccine that was consistent with IgE mediated hypersensitivity. We were unable to determine whether her reaction was due to the recombinant viral-like particles or other constituents of the vaccine such as aluminium hydroxyphosphate sulphate. As she had no history of reactions to yeast, and skin testing for polysorbate 80 gave a negative result, IgE mediated hypersensitivity to these components was unlikely. For females with probable hypersensitivity to the quadrivalent vaccine, immunoblot analysis and measurement of specific IgG and IgE to the individual vaccine components would provide further information.

Our study describes two cases of anaphylaxis after 380 000 doses of the quadrivalent vaccine had been

administered. Although we have a passive surveillance system for reporting vaccine related adverse events in Australia, the quadrivalent human papillomavirus vaccine is a new vaccine and there is a high level of awareness of the importance of reporting adverse events in the school immunisation programme. One study estimated that if 80% of eligible US adolescent females were to receive a saline injection according to the vaccination schedule for human papillomavirus, 3 per 100 000 adolescents would require emergency care for asthma or allergy within 24 hours of vaccination.[12] As allergic symptoms are common, studies of adverse events to the quadrivalent vaccine should take these "baseline" rates into consideration. An Australian human papillomavirus vaccination programme register (www.hpvregister.org.au/), established in August 2008, will facilitate more accurate determination of rates of hypersensitivity reactions not possible from current data sources.

In conclusion, suspected hypersensitivity reactions to the human papillomavirus quadrivalent vaccine require further evaluation to exclude IgE mediated reactions. Most females with suspected hypersensitivity to this vaccine tolerate revaccination. Our clinical recommendation is that females with suspected hypersensitivity to the quadrivalent vaccine should be evaluated before receiving more doses, and any challenges with the same vaccine should be carried out in a supervised setting. Further studies are required to investigate the mechanisms of hypersensitivity to this vaccine.

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