

## The human papillomavirus vaccine and risk of anaphylaxis

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∞ See related research paper by Brotherton and colleagues, page 525

In this issue of *CMAJ*, Brotherton and colleagues<sup>1</sup> report a comprehensive investigation revealing higher than expected rates of apparent anaphylaxis following vaccination with the quadrivalent human papillomavirus (HPV) vaccine in Australian children. The cause of these reactions remains somewhat unclear and needs further investigation. Of note, rates of anaphylaxis, if confirmed, may not be as high in other populations. Further investigations may assist in clarifying differences between the Australian study and other reports.

The use of a review panel with broad expertise in vaccines, allergy, immunology and pediatrics by Brotherton and colleagues and their use of the Brighton collaboration definition of anaphylaxis strengthen the evidence that the reactions were indeed anaphylaxis. This also strengthens their conclusions that the rate of anaphylaxis in the Australian population following HPV vaccination was higher than the rates observed following other vaccinations.

Before concluding that the HPV vaccine is associated with higher rates of anaphylaxis than other vaccines everywhere, cases in other populations should be reviewed. In the United States, 15 cases of anaphylaxis or anaphylactoid reactions following HPV vaccination were reported to the Vaccine Adverse Events Reporting System in 2007. As of July 21, 2008, 11 cases have been reported in 2008. Over 13 million doses of this vaccine had been distributed as of the end of 2007.<sup>2</sup> Although there may be underreporting, the rate of about one case per one million vaccinations is consistent with the rate of anaphylaxis following several other vaccines. Regardless of the true rate, the causes of rare serious adverse events should be identified and vaccines made as safe as possible to maximize benefits and maintain public confidence in vaccines and immunization programs.

Differentiating hypersensitivity reactions from fainting and anxiety reactions can be difficult, especially in busy, school-based clinics. The Clinical Immunization Safety Assessment Network, sponsored by the US Centers for Disease Control and Prevention, has developed guidelines and an algorithm to assist clinicians in the assessment of suspected immediate hypersensitivity reactions and decision-making about administering subsequent doses of vaccine.<sup>3</sup>

Anaphylaxis that occurs within minutes of exposure is usually associated with pre-existing IgE antibodies induced by prior exposure to the allergen. Brotherton and colleagues speculate that the reactions observed could have been due to prior sensitization from yeast proteins in the hepatitis B vac-

### Key points

- The causes of apparent anaphylaxis or anaphylactoid reactions among children in Australia following HPV vaccination are unclear.
- The rate of anaphylaxis following HPV vaccination should be confirmed in other populations.
- These rare but serious adverse events highlight the importance of postlicensure vaccine safety studies and careful management in immunization clinics.

cine or HPV antigens from prior infections. However, 5 of the 7 women developed anaphylaxis after the first dose of HPV vaccine and, for 4 of the women, the results of skin tests were negative for yeast, polysorbate 80 stabilizer and the HPV vaccine. Skin testing performed within a few weeks of exposure could result in false negative tests because of the time lag for host reconstitution of IgE antibodies that were consumed in the reaction. The women in the study by Brotherton and colleagues were tested at least 6 weeks after the reactions, which should have been sufficient time for reconstitution. Testing for serum IgE-specific antibodies can sometimes avoid the pain, inconvenience and risks of reactions associated with skin testing.<sup>4</sup> Brotherton and colleagues appropriately performed skin-prick testing followed by intradermal testing with vaccine diluted to 1:10 and 1:100, because testing with undiluted vaccines can result in high rates of nonspecific reactions leading to the false conclusion that a patient has true hypersensitivity to the vaccine.<sup>5</sup>

The authors also note that polysorbate 80 in the vaccine may have caused anaphylactoid reactions. Anaphylactoid reactions are clinically indistinguishable from anaphylaxis, but IgE antibody is not involved and histamine is released through other mechanisms.<sup>6</sup> However, in several cases where polysorbate 80 was determined to be the cause, the patients had positive reactions to the skin-prick test to this product;<sup>7,8</sup> this was not the case in the study by Brotherton and colleagues. Also, most case reports of anaphylactoid reactions involved receipt of larger doses of polysorbate 80 than the 50 µg present in the HPV vaccine. Further investigations are indicated to identify the true cause of the reactions in Australia.

Specific allergens responsible for causing immediate

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hypersensitivity reactions following other vaccines have been identified, including egg protein in influenza and yellow fever vaccines and gelatin in the measles–mumps–rubella vaccine,<sup>9</sup> but these allergens do not explain all of the cases. Not all children who had immediate hypersensitivity reactions following measles–mumps–rubella vaccination had a positive skin-test result for gelatin.<sup>10</sup>

For people who have had anaphylaxis following a vaccination, subsequent doses are usually contraindicated.<sup>4</sup> However, people at high risk of complications from the disease are faced with the difficult decision to proceed with in-depth evaluations and to possibly administer additional doses of vaccine. Is it safe to administer additional doses of HPV vaccine to patients with negative skin-test results to key vaccine components and the vaccine? Although negative skin-test results can be very helpful, such results do not rule out the possibility of serious immediate hypersensitivity reactions following rechallenge in those who have had immediate hypersensitivity reactions. For patients at high risk of complications from the disease, if a decision is made to proceed with vaccination, some experts recommend using alternative vaccines produced by alternative manufacturers or desensitization under controlled conditions if necessary or both. It would be helpful to know if any of the women in the study by Brotherton and colleagues receive additional doses of any HPV vaccine and if any adverse events occurred.

The HPV vaccine is associated with high rates of fainting in adolescents, which can result in serious head injuries.<sup>11</sup> These adverse events emphasize the need for recommendations to keep adolescents and children under close observation (preferably sitting) for at least 15 minutes after vaccination.<sup>12</sup> The risk of rare, but potentially serious, adverse events such as fainting and immediate hypersensitivity reactions following vaccination should not discourage the administration of this vaccine in school-based clinics, which are an effective means of reaching adolescents. Planning for these programs must include preparation to rapidly detect and treat adverse events, including fainting, anxiety and immediate hypersensitivity reactions. Although most such reactions are uncommon or rare, these events can disrupt otherwise well-planned public health programs.

**Competing interests:** Neal Halsey serves on the data and safety monitoring boards for studies of vaccines sponsored by Merck and for a Harvard investigator conducting a postlicensure safety study of Gardasil in a managed care organization. He has participated in the writing of a manuscript on the immunology of HPV infections sponsored by GlaxoSmithKline, and he has received an honorarium for attending a 1-day meeting during the writing process.

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