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Comments on cow's milk allergy and diphtheria, tetanus, and pertussis vaccines

To the Editor:

Kattan et al¹ report 8 episodes of anaphylaxis that occurred within 60 minutes of administration of DTaP or Tdap vaccines, all of which took place between 2007 and 2010 in children with IgE-mediated milk allergy, within the referral base of the Jaffe Food Allergy Institute in New York. The investigators note correctly that culture media for the commercial production of vaccines against *Clostridium tetani*, *Corynebacterium diphtheriae*, and *Bordetella pertussis* might be supplemented with amino acids derived from bovine milk hydrolysates and use inhibition ELISA data to suggest that 3 lots of DTaP vaccine (from 2 manufacturers) and 5 lots of Tdap vaccine (from 1 manufacturer) contain between 8.1 and 18.3 ng/mL allergenic casein-derived peptides, which were not detected in control lots of viral vaccines. The authors recommend continued immunization with these vaccines for "all children, but advise caution" for patients with severe milk allergy.

Kattan et al¹ perform a valuable service by reporting this novel association, which warrants further study. However, we have concerns about certain aspects of their report and would recommend that readers exercise caution in interpreting these results.

Although the authors state that their "patients were selected based on reports of anaphylactic reactions to vaccines and not because of a history of milk allergy," their institute has a patient base that is enhanced for patients referred for severe food allergy (see <http://www.mountsinaiipa.org/patient-care/practices/allergy-and-clinical-immunology/patient-services/jaffe-food-allergy-institute>), of whom a high proportion would be expected to be allergic to bovine milk. This selection bias is an inherent weakness of drawing conclusions on causation from case reports and would likely overestimate the relationship of food allergy to postvaccine anaphylaxis.

The inhibition ELISA was performed with a rabbit anti-casein polyclonal antiserum rather than with sera from patients with high titers of anti-casein IgE. Patient sera would have provided data of greater relevance to the reactions observed. Furthermore, the ELISA data are presented in the absence of critical information supporting the robustness and reproducibility of the assay, such as the specificities of the rabbit antiserum; the casein used as the antigen coat, positive control, and standard curve; and the performance characteristics of the assay conducted in quadruplicate but presented without CIs. Such information would have provided assurances that the assay is measuring casein-derived proteins in the vaccine lots tested.

Modern vaccines are complex mixtures containing vaccine antigens, including proteins, carbohydrates, and complex conjugates, and additional components, such as adjuvants and residuals from the manufacturing process, and the manufacture of these vaccines is highly controlled. However, allergic reactions have been reported, and anaphylaxis after immunization is an extremely rare but consistent observation.² In spite of numerous studies, the causes and risk factors for these events remain elusive. Thus, for example, although anaphylaxis to influenza vaccine among patients with egg allergy has suggested a causative role for residual ovalbumin in the administered product, the rate of postvaccine allergic events appears to be no greater among recipients with egg allergy than among the population without egg allergy.^{3,4}

The authors state that they "are not aware of prior reports linking milk contamination to anaphylaxis from these vaccines." Likewise, prospective surveillance of the Vaccine Adverse Event Reporting System by the US Food and Drug Administration has not yielded a safety signal for anaphylaxis in patients with milk protein allergy. We plan further analyses of Vaccine Adverse Event Reporting System data, as well as product-based assessments of possible allergen content of United States-licensed DTaP and Tdap vaccines. At this time, we believe that the currently available data, including those described by Kattan et al,¹ do not support the hypothesis that severe milk allergy might be associated with postimmunization anaphylaxis caused by residual bovine milk allergen in DTaP or Tdap vaccines. Milk allergy is common, appearing in as many as 2.5% of young children,⁵ and is self-diagnosed in even greater numbers in children and teens. If, as a consequence of this report, the DTaP immunization rate of patients with real or perceived milk allergy decreases, then the risk of disabling and even fatal illness within this large group will needlessly increase.⁶ Health care providers are urged to encourage timely immunizations, as recommended, for all eligible recipients.

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