

Reply

To the Editor:

We thank Slater et al¹ for their comments regarding our observation that 8 patients reporting anaphylaxis to Tdap and DTaP vaccines all had severe cow's milk allergy and that the vaccines we tested had residual trace amounts of casein, as might be expected from the manufacturing process.² We are very pleased that the US Food and Drug Administration plans to investigate this issue further.

Regarding the inhibition ELISA, we did not provide additional details because of the space limitations of the brief article. The assay is substantially similar to one that we previously published,³ with additional optimization. The rabbit anti-casein antibodies (a gift from Ross Laboratories, Columbus, Ohio) were affinity purified, and coating and inhibition were done with purified casein (87% to 94%; Sigma-Aldrich, St Louis, Mo). The reproducibility of the assay was confirmed by repeating the standard curve (7 times) and vaccine samples, both samples of interest and negative controls. Only the linear portion of the standard curve was used for calculating the concentration of casein. A mixture (1:1) of rabbit anti-casein antibody with blocking buffer alone was used to establish the background total absorbance of our assay. The negative results of the "negative" control samples ("negative" with respect to the vaccine package inserts not indicating reagents with potential casein residues) also indicate the specificity of our assay. Additionally, assay development showed no competition between coated casein and the secondary antibody, horseradish peroxidase-labeled goat anti-rabbit IgG (Sigma-Aldrich). For Tdap and DTaP vaccine testing, all wells had optical densities corresponding to positive values, with coefficients of variation ranging from 1.6 to 30.5. In distinction, all negative controls had optical densities similar to total absorbance out of the range of our standard curve. We are therefore confident that we are measuring a trace amount of residual casein in the vaccines. Unfortunately, however, we did not have serum samples from the affected patients to test against the vaccines.

We agree with Slater et al¹ that our patient population is biased with regard to being enriched for food allergy and that conclusions on causation cannot be reached from a case series. Indeed,

we emphasized the fact that many patients with severe milk allergy clearly tolerate the vaccines. Our main message is that our observation raises a concern, and we suggested that further studies are needed. Although we have not proved that residual milk protein is the cause of the anaphylactic reactions, we believe that the case series is compelling for a need to address the concern with additional studies. For example, over the same period, we did not identify any other patient in our practice with anaphylaxis to the vaccines who did not have a milk allergy; our patient base includes many subjects with other severe food allergies without cow's milk allergy. Nonetheless, the risk for those with cow's milk allergy, which still requires verification regarding cause, is apparently low, and for now, we simply suggest caution and not withholding of vaccinations.

Jacob D. Kattan, MD

George N. Konstantinou, MD, PhD, MSc

Amanda L. Cox, MD

Anna Nowak-Węgrzyn, MD

Gustavo Gimenez, BA

Hugh A. Sampson, MD

Scott H. Sicherer, MD

From the Elliott and Roslyn Jaffe Food Allergy Institute, Mount Sinai School of Medicine, New York, NY. E-mail: Scott.Sicherer@mssm.edu.

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