

CORRESPONDENCE

Maintaining Safety with SARS-CoV-2 Vaccines

TO THE EDITOR: In the review article by Castells and Phillips on vaccines for the prevention of infection with SARS-CoV-2 (published on Dec. 30 at NEJM.org),¹ the authors describe cases of anaphylaxis associated with the Pfizer–BioNTech messenger RNA (mRNA) vaccine. The estimated incidence of anaphylaxis is 1 in 100,000 injections, as compared with an expected incidence of 1 in 1 million injections.²

The incidence of anaphylaxis after vaccination with the quadrivalent human papillomavirus (HPV) vaccine (Gardasil) has been estimated at 1 in 190,000 injections³; this incidence is similar to that reported for the Pfizer–BioNTech vaccine. Polysorbate 80 is an excipient in Gardasil, and we identified polysorbate 80 as the culprit in a case of anaphylaxis that occurred in a young girl after the third intramuscular administration of that vaccine.⁴

Castells and Phillips note that the implications for the future use of SARS-CoV-2 vaccines, which are commonly formulated with polysorbate 80 (with a structure similar to that of polyethylene glycol [PEG]), are unknown. Allergists should be aware that cross-reactive immediate hypersensitivity to macrogols (PEGs) and polysorbates can occur. We have reported⁵ a case of multiple drug reaction due to hypersensitivity to PEGs of a wide variety of molecular weights, from PEG 80 to macrogol 6000.

Giovanni Rolla, M.D.

Luisa Brussino, M.D.

University of Turin
Turin, Italy
grolla@mauriziano.it

Iuliana Badiu, M.D.

Mauriziano Hospital
Turin, Italy

No potential conflict of interest relevant to this letter was reported.

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1. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med* 2021;384:43-9.

2. Stone CA Jr, Rukasin CRF, Beachkofsky TM, Phillips EJ. Immune-mediated adverse reactions to vaccines. *Br J Clin Pharmacol* 2019;85:2694-706.

3. Kang LW, Crawford N, Tang MLK, et al. Hypersensitivity reactions to human papillomavirus vaccine in Australian school-girls: retrospective cohort study. *BMJ* 2008;337:a2642.

4. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep* 2012;2012:bcr0220125797.

5. Badiu I, Guida G, Heffler E, Rolla G. Multiple drug allergy due to hypersensitivity to polyethylene glycols of various molecular weights. *J Investig Allergol Clin Immunol* 2015;25:368-9.

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THE AUTHORS REPLY: Rolla et al. cite a retrospective cohort study of 380,000 doses of HPV vaccine.¹ That study included one case in which the timing of symptom onset (15 to 20 minutes) was consistent with anaphylaxis. The article by Badiu et al.² provided evidence of potential reactivity to polysorbate 80 that is present in both the influenza vaccine (Fluarix) and the HPV vaccine. However, the person with the reaction described by Kang et al.¹ had a positive skin test with the HPV vaccine but a negative test with polysorbate 80 and was never rechallenged. In a prospective study of 600,558 HPV vaccine doses administered, only one reported case of anaphylaxis was noted.³

Whether the PEG 2000 component of mRNA SARS-CoV-2 vaccines is implicated in anaphylaxis and other immediate reactions has not been established. Polysorbates are excipients in several SARS-CoV-2 vaccines that are under development as well as in at least 20 vaccines licensed in the United States, where anaphylaxis has not been a prevalent signal.⁴

Allergy assessment that involves skin testing and challenges to PEG and derivatives including polysorbates is warranted. Research is under way to help define the population at risk and the mechanism or mechanisms of anaphylactic reactions to SARS-CoV-2 mRNA vaccines, as well as safe vaccine and medication use in this population.⁴

Mariana C. Castells, M.D., Ph.D.

Brigham and Women's Hospital
Boston, MA
mcastells@bwh.harvard.edu

Elizabeth J. Phillips, M.D.

Vanderbilt University Medical Center
Nashville, TN

Since publication of their article, the authors report no further potential conflict of interest.

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1. Kang LW, Crawford N, Tang MLK, et al. Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: retrospective cohort study. *BMJ* 2008;337:a2642.
2. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep* 2012;2012:bcr0220125797.

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4. Stone CA Jr, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract* 2019;7(5):1533.e8-1540.e8.

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