

The COVID-19 Pandemic in 2021: Avoiding Overdiagnosis of Anaphylaxis Risk While Safely Vaccinating the World



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In this issue, Banerji et al¹ outline an approach to allergic reactions from mRNA vaccines, and provide a review of an evolving situation. As the authors emphasize, we are living and practicing in uncertain and unprecedented times. Their review serves to provide an up-to-date understanding of the challenges faced not only by the allergy community but by broader international public health efforts to combat the pandemic.

It is important to realize that as current knowledge evolves, guidance will likely be conditional—and may change as our understanding of the pandemic and coronavirus disease 2019 (COVID-19) vaccines develops. Particularly in light of present uncertainties and a somewhat volatile future, a judicious approach involves decision-making grounded in understanding lessons learned from previous experience with vaccine

anaphylaxis. Such lessons can be applied to approaches to vaccine skin testing, management of known excipient allergy, vaccine graded challenge, and vaccine deferral during the COVID-19 pandemic. As Banerji et al discuss, any approach must balance risks and benefits—both of preventing COVID-19 on patient and population levels and mitigating risk for anaphylaxis. Navigating these somewhat competing priorities remains a challenge. As allergists, we must remain focused on risk assessment, cost-effectiveness, broad public health implementation, and consideration of the potential unintended consequences of screening and vaccine avoidance. In this regard, there are several important points to highlight when approaching patients who are concerned about allergy risk and COVID-19 vaccination.

First, when considering the many uncertainties in COVID-19 vaccine adverse reactions, one thing is clear—at present it is unlikely that all the reported reactions to the mRNA vaccines are IgE-mediated. This reality may fundamentally alter the necessity of allergy-based risk stratification to some degree.¹⁻⁴ Indeed, a

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Conflicts of interest: M. Greenhawt has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrimmune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Nutricia, Kaleo Pharmaceutical, Nestle, Acquestive, Allergy Therapeutics, Pfizer, US World Meds, Allergenix, Aravax, and Monsanto; is a member of the Scientific Advisory Council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune, DBV, Before Brands, multiple state allergy societies, the American College of Allergy, Asthma, and Immunology, and the European Academy of Allergy and Clinical Immunology; is an associate editor for *the Annals of Allergy, Asthma, and Immunology*; and is a member of the Joint Taskforce on Allergy Practice Parameters. E. M. Abrams is on the Steering Committee of Food Allergy Canada's National Food Allergy Action Plan; is a collaborator with the Institute for Health metrics and Evaluation; and has received moderator/speaker fees from AstraZeneca (AZ), GlaxoSmithKline (GSK), and Sanofi; is on the National Advisory Board for Food Allergy Canada; and is on the National Food Allergy

Action Plan Action Steering Team for Food Allergy Canada. J. Oppenheimer declares the following: Research/Adjudication: AZ, GSK, Sanofi, and Novartis; Consultant: GSK, AZ, and Sanofi; Associate Editor: *the Annals of Allergy, Asthma, and Immunology, AllergyWatch*; Section Editor: *Current Opinion of Allergy*; Royalties: Up to Date; and Board Liaison American Board of Internal Medicine (ABIM) for American Board of Allergy and Immunology (ABAI). T. K. V. Leek has served on advisory boards and received honoraria from Aralez, Bausch Health, and Pfizer. D. P. Mack is a member of the Board of Directors for the Canadian Society of Allergy and Clinical Immunology; serves on the Editorial Board of *the Journal of Food Allergy*; has provided consultation and speaker services for Pfizer, Aimmune, Merck, Covis, and PEDIAPHARM; has been part of an advisory board for Pfizer and Bausch Health; and is an investigator for ALK. A. G. Singer has no conflicts to disclose. M. Shaker is a member of the Joint Taskforce on Allergy Practice Parameters; has a family member who is CEO of Altrix Medical; and serves on the Editorial Board of *the Journal of Food Allergy and the Annals of Allergy, Asthma, and Immunology*.

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complete understanding of the underlying pathophysiology of the reported COVID-19 vaccine adverse reactions is yet to be determined. As noted by the authors, although an event may be reported as allergic, and a particular excipient identified as a potential culprit, when reviewing the available evidence regarding symptom presentation in these cases, many patients have reported atypical features. These features have included a number of highly subjective symptoms, which may be explained at least in part through a vasovagal or non-immune-mediated mechanism.^{1,2} Although anaphylaxis is not a requirement for epinephrine use, similarly a response to epinephrine does not necessarily imply the presence of an allergic reaction as etiology. Anaphylaxis is a *clinical diagnosis* established by the *timing and nature of symptoms*.³ As Banerji et al¹ highlight, the differential diagnosis of vaccine-related reactions is not limited to IgE or other immune-mediated phenomena. If such events are not definitively allergic, it raises questions about the unintended consequences of any strategy aimed at preemptive screening to prevent vaccine anaphylaxis.⁶ We need better understanding of adverse reactions to COVID-19 vaccines, and we as allergists need to be discerning in our investigation of these events, rather than simply accepting self-reported encounters or media coverage as bona fide evidence of an allergic reaction. We would urge restraint in concluding that vaccine anaphylaxis to this agent is anything more than a statistically rare event. Moreover, even assuming these reported events were indeed immune-mediated, the broader population perspective must be considered. Specifically, if we are to presume every case considered to be anaphylaxis in a recent MMWR report is correctly classified, 21 events out of nearly 2 million doses remain an exceedingly low absolute risk.⁷ In this setting, the contrast between relative and absolute risk becomes important. Although the increase from 1.3 to 11.1 cases per million is a large relative risk, the absolute risk increase is quite low.⁷ In fact, this remains still much lower than the disclosed hypersensitivity rate of 0.1% stated in the emergency use authorization (1000 cases per 1 million vaccinations) for all-comer hypersensitivity.^{8,9}

Second, there is speculation, but not certainty, that polyethylene glycol (PEG) is a definitive culprit allergen. Although there remains no clear proof that PEG is causative at present, responses to date in the United Kingdom, Canada, and the United States have restricted vaccination of individuals with a history of previous PEG reactions from parenteral medication.^{3,4,10} Although this is understandable in the context of evolving and rapidly changing information, it is presumptive at present and potentially unnecessary. It is also worthwhile to consider past experience with vaccine excipients constituting a risk of an allergic reaction. Indeed, there is a mixed and somewhat inglorious recent history with respect to well-intentioned risk assessment of key vaccine excipients in excipient-allergic individuals, which has led to unnecessary exclusion and declaration of risk. For example, modern influenza vaccine contains egg protein. For years, guidance recommended caution and restricting influenza vaccination in egg-allergic individuals, only to discover that this risk was unfounded for modern influenza vaccines, with no risk over baseline to the egg-sensitized recipient, resulting in unnecessary avoidance of the vaccine. Furthermore, egg is a far more ubiquitous allergen than PEG, and it is worthwhile to recall this experience with egg and influenza vaccine (as well as with measles, mumps, and rubella [MMR] vaccine, which was handled similarly).^{5,6} However,

particularly in the context of the MMR vaccine, it is also important not to completely disregard any potential role of excipients in triggering allergic reactions to vaccines, and gelatin content in MMR vaccine is a notable example that can be mitigated and managed by allergists to successfully achieve subsequent vaccination.⁵ Importantly, perception of risk becomes anchored with earliest available information, and is very difficult to retroactively change, in particular when professional organizations declare an excipient a culprit without firm evidence of causality, and recommend altered management for particular vaccine recipients. This has been the case with some COVID-19 vaccine recommendations, which is concerning, given the lack of clear evidence to inform practice. We can ill afford additional communication missteps during the current pandemic. The bottom line is that even in excipient-allergic persons, it is rare that the excipient concentration is of sufficient threshold to provoke an allergic reaction deeming vaccine deferral necessary, and we may very well cause more harm through preventing their vaccination than we do by preventing an allergic reaction to the vaccine (if efforts at risk stratification even have the ability to mitigate anaphylaxis). From a risk communication perspective, it is important to anchor guidance in robust and accurate information. We must be cautious to avoid slipping backward into “presuming danger until proven safe” because this has the possible unintended consequence of contributing to vaccine hesitancy, or in the worst case, chasing the wrong risk factor (eg, egg and MMR/modern influenza vaccines). We should learn from the mistakes of the past in this regard because the stakes are too high with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to repeat the same course.

Third, even assuming PEG is the allergen, there is historical difficulty in consistently and accurately assessing anti-PEG IgE through skin testing. Again, the literature on PEG allergy is small, albeit growing, but the one commonality in all the small case reports has been that skin testing does not always produce wheal and flare in recipients with true PEG allergy.¹¹⁻¹⁴ That inconsistency speaks to poor reliability of the substance as a skin testing allergen when applied at full concentration, and decreases confidence in being able to use the results for clinical decision making.¹⁵ Presently, there is no standardized skin test material for PEG, and in the most basic situation we are unable to definitively determine that (a) any wheal and flare produced from application is both not the result of irritation AND unequivocally indicates the presence of IgE and (b) the same application producing the absence of a wheal and flare unequivocally means no IgE is present. Although a basic tenet in the field of allergy, this lack of reliability is why allergens must be standardized, to allow us to inform clinical decisions with confidence. As simple as it is to apply a skin prick test to any agent, we have to understand what the results mean—particularly if we are to create policy surrounding these test results and implement it on a broad scale. This is further complicated only if the skin testing approach adds multiple medicinal agents to which patients have not demonstrated an allergy but that contain PEG or polysorbates—which can further confuse interpretation of which component of any given mixture may be responsible for any wheal or flare identified, notwithstanding whether this even represents IgE recognition. This creates opportunity cost in the form of health care utilization and resultant vaccination delay. Moreover, we do not know the population prevalence of PEG allergy with high enough certainty to clearly establish predictive

values, or have widespread enough understanding of PEG skin testing to establish positive and negative likelihood ratios. As a result of this uncertainty, our interpretation of the value offered in clinical decision-making of a “positive” skin test response to a nonirritating concentration of PEG differs somewhat from Banerji et al. The lack of proven reliability of PEG skin testing suggests clinicians exercise caution if basing decisions on a “positive” or “negative” result, because there is an absence of any positive predictive value for a nonstandardized allergen testing agent without a discernable population prevalence. In such an instance, the only thing that could be established would be a positive or negative likelihood ratio, but even that is lacking for PEG skin testing. Although this situation is not unique to PEG, the lack of a clearer understanding of predictive values warrants cautious interpretation of results, particularly if recommending vaccine be withheld in individuals with positive skin test results. At least at present, an approach of universal vaccine deferral in patients with positive skin test results for PEG could risk more harm than benefit. However, if testing is pursued, we do agree with Banerji et al that shared decision-making is a critical component in the management of the PEG-sensitized patient. This must involve a close linkage to an opportunity for allergist-supervised graded vaccine challenge, which is key to providing safe vaccination that is consistent with individual values and preferences. Still, we would urge restraint in indiscriminate testing to PEG, given the low certainty of any evidence of benefit and significant risk that testing results could be misinterpreted.

Fourth, although prevaccination risk-stratification medical questionnaires provide a framework to move forward with vaccination and address some stakeholder concerns, questionnaires also risk added medical complexity that could create confusion and dilute vaccination messaging. As Banerji et al highlight, there is no clear evidence that past history of anaphylaxis, medication allergy, food allergy, asthma, allergic rhinitis, or family history produces an incremental risk for an adverse reaction of any kind to COVID-19 vaccination. This fact does raise questions about the value of requiring longer observation of patients with previous “potential” anaphylaxis to culprits that are not present in COVID-19 vaccines—particularly if more prolonged observation decreases implementation of broad vaccination through reduced acceptability of vaccination by patients, or reduced broad feasibility at a population level.¹ The only contraindication to COVID-19 vaccination, as currently stated in both the United States and Canada, is an allergy to the actual vaccine or excipient ingredient. Importantly, any population screening approach for sensitization to excipients is not justified, has no validity, is not necessary before COVID-19 vaccination, is likely poorly feasible and sustainable on a broad scale, and has the potential to reduce vaccine acceptance and rollout. As allergists, we must guard against a tendency of “screening creep” to populations without severe allergic reactions to parenteral PEG-containing agents who can simply receive vaccination. Fortunately, for patients who experience an adverse reaction to any vaccination, a simple algorithm exists that can effectively allow vaccination through graded challenge, if that is felt to be necessary.⁵ Graded dose challenges to COVID-19 vaccines have been endorsed under allergist supervision for patients with a suspected allergic reaction to the COVID-19 vaccine in preliminary guidance by the European Academy of Allergy and Clinical Immunology and the Canadian Society of Allergy and Clinical Immunology.^{16,17} This approach is

consistent with decades of experience in managing vaccine allergy; however, as for most vaccines, the safety and efficacy of this approach specifically as it relates to newly released COVID-19 vaccines is unknown or not informed by high certainty evidence.⁵ It is also important for allergists to note that confidence is generally quite low in the ability of premedication with antihistamines and/or glucocorticoids to prevent anaphylaxis, and such an approach has not been recommended previously in evaluation and management of vaccine hypersensitivity.^{5,18} Again, we would urge restraint in presuming that previous history of a reaction to an injectable medication is a risk for COVID-19 vaccine anaphylaxis, and strongly caution against deferring, delaying, or requiring additional supervision for vaccinating such individuals. Although Banerji et al highlight the fact that 17 of 21 cases of anaphylaxis reported by the Centers for Disease Control and Prevention on January 6, 2021, had an imprecise history of preexisting “allergy” (including “bee stings,” “sulfa drugs,” “cats and dogs,” “iodinated contrast media,” and “hydrocodone, nut”), we do not know the number of the some 2 million other individuals who were successfully vaccinated without incident who may have also shared this history.⁷ Here, it is important to not be deductively selective in presuming risk from a small group of individuals without considering the larger experience from the remainder of cases.

Lastly, comparative risk must be properly assessed, and our actions toward anaphylaxis risk-reduction should be consistent. Most importantly, we must keep in mind that COVID-19 had already infected 82 million individuals and cost 1.79 million lives at the close of 2020.¹⁹ This pales the comparison of morbidity and mortality caused by anaphylaxis, and we need to be honest and open about that. The pandemic is the much larger and more pressing public health risk. Patients are seen in allergy clinics every day with an array of conditions that place them at risk for allergic reactions, anaphylaxis, and even death. However, it must be remembered that many of these conditions carry a risk of fatality much lower than risks patients take in everyday living—risks that even include driving to the doctor’s office for that very appointment, or even being struck by lightning. One example of comparative anaphylaxis risk resonates with all allergists. Every day, in nearly every allergy practice in the United States, we inject persons with known allergic sensitivity to a mixture of allergens in the form of immunotherapy, bearing a known risk of reactions and even fatality.²⁰ We are confident in the safety of allergen immunotherapy because we (a) understand the risk context and (b) manage this risk quite effectively. This example is imperfect because immunotherapy relates to targeted and managed immunologic phenomenon. However, the point is that allergists are trained and experienced to provide needed medications and therapies to patients at risk for anaphylaxis—and it is very, very rare that we are unable to provide a critical medication (or vaccine) to a patient at risk. And whether it be through immunotherapy, drug desensitization, or graded challenge, allergists have the tools to provide therapies in spite of (and sometimes because of) demonstrable allergen sensitization. Even assuming an at-risk population can be identified, that PEG is a culprit for reactions, and that PEG skin testing is reliable and predictive, providing an mRNA vaccine containing PEG to someone with a positive skin test result to PEG may not be a larger risk than we manage routinely in our clinics. Worse, without any data to suggest, preemptively, that PEG-allergic individuals (or individuals with some previous history of

anaphylaxis to a medication) consistently and reliably do not tolerate these mRNA vaccines, we may be instilling our own values in predetermining what is a greater risk for our patients if, at minimum, graded vaccine challenge is not offered. If we deny any vaccination opportunity flat-out, on the basis of our own concerns, we bypass the shared decision-making process and the outcome may reflect neither the medical reality of the situation nor the desires of the patient.

It would be harmful to restrict vaccination beyond presently labeled contraindications during the COVID-19 pandemic without a higher burden of proof. For individuals with an a priori documented allergy to the mRNA vaccine, an approach similar to that outlined in the 2012 vaccine parameter may be appropriate.⁵ If vaccine quantities are insufficient for skin testing (which is a present issue given rationed supply in the early phase rollout of the vaccination campaign), a graded challenge may be a very reasonable approach for a patient with documented history of previous mRNA vaccine anaphylaxis, to ensure both safety and ability to receive the vaccine.^{5,16,17} Even presuming patients can wait for an alternative vaccine (also a decision where we could be instilling our values onto the patient), such as an adenovirus vector vaccine, there is no guarantee at the moment that it will be safer or as effective as other vaccines. More to the point, such delay could facilitate overdiagnosis of anaphylaxis risk. Should anaphylaxis occur, effective treatment is rapidly available. We are unable to say this with the same certainty if an unvaccinated individual was to contract COVID-19.

We must be vigilant to avoid adding complexity through overdiagnosing anaphylaxis risk to a global vaccine effort that is already facing unprecedented challenges of distrust and disinformation campaigns. As allergists, we must provide a clear, evidence-based, and balanced perspective on anaphylaxis risk. The world is looking to our expertise, as we rise to meet this moment. This is a virus that has killed millions worldwide, whereas only a very small number of patients have suffered from reactions following vaccination, none of which have led to a fatality. The medical community has begun to evaluate these reactions and respond. The guidance provided by Banerji et al is an example for a starting approach, and we wish to supplement how the allergist-immunologist can approach this through discussing some additional contextualized issues to consider in weighing options for how to proceed. While we wait for evolving science to further inform our practice, we applaud the incorporation of shared decision-making into COVID-19 vaccination, to make sure the patient's values and preferences are at the forefront of critical efforts to immunize the world and turn the tide on a devastating pandemic.

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