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How important is the second dose of the COVID-19 mRNA vaccine?

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To the Editor:

The current data and lack thereof for allergy guidance on coronavirus disease 2019 (COVID-19) mRNA vaccines was outlined beautifully by Banerji et al[1] and Greenhawt et al.[2] As allergists create algorithms and testing protocols to evaluate patients who have had possible allergic reactions to the first dose of the Pfizer/BioNTech or Moderna vaccine, it also falls to allergists to counsel patients on the undefined benefit of the second dose.

Booster doses are intended to promote B-cell affinity maturation, increase neutralizing antibodies, and expand the memory T-cell pool. In practice, both COVID-19 mRNA vaccines confer excellent short-term protection starting 2 weeks after the first dose, before second-dose administration. Between days 15 and 21 after the first dose, symptomatic infections were reduced by almost 90% among Pfizer trial participants.[3] Among Moderna trial participants who received a single dose only, vaccine efficacy was 92% starting at day 14, with a median follow-up of 28 days.[4] Efficacy might suffer against variants such as B.1.351, and whether this difference would be affected by delaying a second dose is unknown.

In the short-term, the infection-related risk of delaying a second dose of mRNA vaccine by several weeks may be low. For those who experience a possible first-dose reaction, such a delay may allow patients time to gather information to guide a second-dose decision. Studies are ongoing on degree and duration of protection with a single dose, safety and efficacy of mixing vaccines (eg, adenovirus vaccine after mRNA vaccine), and impact of vaccine intervals on protection against or development of new variants. As allergists pursue various evaluation algorithms, we will find out more about the predictive value of skin testing, likelihood of second reactions, and efficacy of vaccines given by graded challenge.

Adenovirus vector vaccines may change allergists' algorithms. Johnson & Johnson has obtained emergency use authorization for its vaccine as a single dose, and AstraZeneca's vaccine data are encouraging for single-dose efficacy for at least 3 months. Combined data from AstraZeneca trials showed vaccine efficacy of 76% after a single dose, with stable antibody titers to day 90, compared with 67% overall efficacy after 2 doses, with noted demographic differences between subgroups. Among those who received 2 doses, prolonging the interval between doses to 3 months was associated with greater vaccine efficacy, at 82% and 55%, with dose intervals of 12+ weeks and less than 6 weeks, respectively.[5]

Motivated patients seeking clearance for a second mRNA vaccine dose tell us they want this "life-saving" protection. Yet we do not know whether the second dose confers substantial additional protection against hospitalization and death.

For the general population, both mRNA vaccine doses should be given as studied, supply permitting. For patients whose first-dose reactions have raised concerns about second-dose safety, the limited data on short-term single-dose efficacy should be weighed along with exposure risk and reaction severity.

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Reply to "How important is the second dose of the COVID-19 mRNA vaccine?"

To the Editor:

We thank Liu[1] for a thoughtful commentary on recent guidance for coronavirus disease 2019 (COVID-19) vaccination.[2,3] Liu[1] raises several important points that highlight uncertainties surrounding the COVID-19 vaccination effort, suggesting that for some patients who experience a severe allergic reaction to a first mRNA vaccine dose, a second vaccine dose may be deferred or delayed in light of limited evidence demonstrating good short-term efficacy of a single dose.[1,4-6] Our understanding continues to rapidly evolve on this topic. For example, a recent study from the Sheba Medical Centre reported an 85% (95% CI, 71%-92%) reduction in symptomatic COVID-19 cases 15 to 28 days after the first dose of the Pfizer-BioNTech vaccine.[5] This reduction in symptomatic COVID-19 infection is improved from an original estimate for first-dose vaccine efficacy of 52.4% reported by Polack et al,[7] and may differ as a result of timing of the measurement. When considering the ratio of confirmed cases of COVID-19 illness in active versus placebo groups from Polack et al, Pfizer-BioNTech vaccine efficacy has been estimated at 92.6% beginning 14 days after dose 1 to before dose 2.[6] Indeed, this rate is similar to the first-dose efficacy rate of 92.1% reported for the Moderna vaccine.[6,8] Still, uncertainty remains regarding single-dose mRNA vaccine protection, as a recent population-based Israeli study including 596,618 vaccinated persons estimated single-dose effectiveness against documented infection at 14 to 20 days at 46% (95% CI, 40%-51%) for the Pfizer-BioNTech vaccine, with

estimates of protection reaching 74% (95% CI, 56%-86%) for hospitalization and 72% (95% CI, 19%-100%) for preventing death.[9]

It must be acknowledged that the duration of single-dose mRNA vaccine efficacy is presently unknown.[4] Indeed, even the longer-term efficacy of the full COVID-19 mRNA vaccine series is unclear, and the question of whether or not to routinely defer second vaccine doses in an effort to more rapidly mobilize first vaccine doses to combat the COVID-19 pandemic has been a subject of debate.[4] Given that all COVID-19 vaccine products remain unlicensed and are currently administered under emergency use authorizations (EUA), it may be reasonable to assume that administration per EUA guidance would be optimal. Although, now more than ever, it is important to realize the good is not the enemy of the perfect. Assuming durable high first-dose mRNA vaccine protection is achievable, it could be reasonable to defer a second dose in a patient at high risk for COVID-19 mRNA vaccine anaphylaxis, though this remains a difficult decision to contemplate, rife with uncertainty from widely ranging preliminary estimates regarding the incremental benefit of the fully recommended vaccination series.[10] Recent modeling suggests that deferral of a second COVID-19 mRNA vaccine dose could leverage optimal health and economic outcomes when durable first-dose protection is very high and rates of vaccine anaphylaxis are significantly elevated above baseline risk.[10] For example, assuming durable first-dose protection reaches 90% and a second dose offers only 5% protection, second-dose deferral would be cost-effective if anaphylaxis risk exceeded 0.13%; this frequency is much greater than the risk of anaphylaxis reported in the general population but may be lower than the risk perceived by the allergist-immunologist evaluating a patient after anaphylaxis with a first dose.[10-13] However, at lower rates of first-dose protection, the importance of a second dose may become more significant, and deferral may cause more harm than benefit, even in patients with a risk of COVID-19 mRNA vaccine anaphylaxis well above that of the general population.[10] As an alternative to a second mRNA vaccine dose, guidance has been suggested that a single dose of a COVID-19 viral vector (ie, Janssen) vaccine may be considered at a minimum interval of 28 days from the mRNA dose in persons with a contraindication to a second COVID-19 mRNA vaccine dose. In patients with a contraindication to a COVID-19 mRNA vaccine (considered a precaution to the COVID-19 viral vector vaccine), allergist-immunologist referral should be considered and such administration should occur under the supervision of a provider capable of managing anaphylaxis.[14]

Liu has provided valuable insight into a complex question of second-dose COVID-19 mRNA vaccine deferral. Such an option, as part of shared decision making with the patient, would require careful consideration and would be a highly contextual decision, conditional on a rapidly evolving understanding of best vaccination practices and careful values clarification on behalf of the informed patient. Although most patients referred for a possible vaccine reaction will be able to receive a second vaccine dose safely, for those at very high relative risk for anaphylaxis, the decision to defer or forego the second dose could be a reasonable option to discuss, if indeed protection from a first dose is reliable in the longer-term. Still, for greatest efficacy, providing vaccinations as recommended in each EUA would be preferred if possible. Information on durability of first-dose responses overall, as well as in those who have had mRNA vaccine anaphylaxis or previous COVID-19, and the local availability of additional COVID-19 vaccine options[14,15] will also help guide these decisions.

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Conflict of interest: M. S. 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*. E. Phillips reports grants from the National Institutes of Health (grant nos. P50GM115305, R01HG010863, R01AI152183, R21AI139021, and U01AI154659) and from the National Health and Medical Research Council of Australia; receives Royalties from UpToDate and consulting fees from Janssen Vertex, Regeneron, and Biocryst; is codirector of IIID Pty Ltd, which holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity; and has a patent pending for Detection of Human Leukocyte Antigen-A*32:01 in connection with Diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms without any financial remuneration and not directly related to the submitted work. 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. J. Oppenheimer declares the following: Research/Adjudication: AZ, GSK, Sanofi, and Novartis; Consultant: GSK, AZ, and Sanofi; Associate Editor: *Annals of Allergy, Asthma, and Immunology*, AllergyWatch; Section Editor: *Current Opinion of Allergy*; Royalties: UptoDate; and Board Liaison American Board of Internal Medicine for American Board of Allergy and Immunology. T. L. 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 and has been part of an advisory board for Pfizer and Bausch Health. M. Greenhawt has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrommune, 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, Allergenis, Aravax, and Monsanto; is a member of the Scientific Advisory Council for the National Peanut

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Protective effects of eosinophils against COVID-19: More than an ACE(2) in the hole?

To the Editor:

We read with great interest the recent publication by Ferastraoaru et al[1] in the January 2021 issue of *JACI: In Practice* that reported type 2 high asthma with eosinophilia is protective against severe coronavirus disease (COVID-19). As the authors note, this protective effect may be due to reduced viral binding and propagation in type 2 high asthmatic airways as the result of downregulated expression of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) receptor, angiotensin-converting enzyme 2 or ACE(2), on airway epithelium. It is notable, however, that many prior studies have reported antiviral and immunomodulatory functions of eosinophils in humans and in animal models, which in light of the present findings, are potentially complementary or alternative mechanisms that explain this effect. Eosinophils express a variety of pattern recognition receptors capable of detecting viral RNA genomes, including Toll-like receptors 3 and 7, RIG-like receptors, and NOD-like receptors.[2] Once activated, eosinophils release mediators with direct antiviral activity such as eosinophil cationic protein and eosinophil-derived neurotoxin, whose ribonuclease activity degrades viral RNA genomes, and nitric oxide, which has been shown to reduce infectivity of 2 other RNA respiratory viruses, parainfluenza virus and respiratory syncytial virus.[2] Eosinophils also produce T_H1-related cytokines involved in antiviral defense, including IFNγ and IL-12, and they express major histocompatibility complex class 1 and 2 molecules that enable antigen presentation and recruitment of viral-specific CD8 T cells to the lung.[2]

Although much of our mechanistic understanding of eosinophil's antiviral effects is derived from *in vitro* studies of human and mouse eosinophils, several experimental observations support the concept that eosinophils are antiviral *in vivo* as well. For example, mice and guinea pigs with allergen-induced airway eosinophilia have lower titers of parainfluenza virus in the lung 4 days after infection,[3,4] and transgenic mice with eosinophilia due to IL-5 overexpression also exhibit accelerated viral clearance.[4] In influenza-infected mice, adoptive transfer of eosinophils into airways reduces viral titers,[5] whereas double transgenic eosinophil-deficient mice that overexpress IL-5 lack this antiviral response, indicating that eosinophils specifically, not IL-5, mediate the antiviral effect.[4] Similarly, in a study of experimental rhinovirus infection in humans, mild asthmatics treated with the anti-IL5 antibody mepolizumab had higher nasal viral titers than placebo-treated individuals, suggesting that eosinophil's antiviral functions are conserved between animals and humans.[6]

As both eosinophils and viral infections are important causes of asthma attacks, eosinophil activation in virus-infected airways is likely a double-edged sword capable of causing both harm during asthma exacerbations triggered by seasonal respiratory viruses and protection against serious and fatal infections from pandemic SARS-CoV-2. Indeed, despite a common evolutionary lineage with seasonal coronavirus variants, SARS-CoV-2 and prior pandemic coronaviruses, Middle East respiratory syndrome and SARS, share unique genomic features that account for their immunogenicity. Given that higher SARS-CoV-2 titers are associated with increased mortality,[7] eosinophil's ability to directly and indirectly attenuate viral replication may protect against development of a runaway inflammatory response that underlies the onset of severe COVID-19 disease.

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