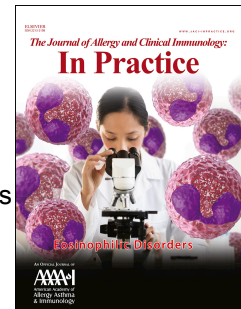


Journal Pre-proof

The importance of a timely second dose of the 2021 COVID-19 mRNA vaccine depends on the protection afforded by a first dose and subsequent risk of anaphylaxis

Marcus Shaker, MD MSc, Elizabeth Phillips, MD, Kimberly G. Blumenthal, MD, MSc, Elissa M. Abrams, MD, Aleena Banerji, MD, John Oppenheimer, MD, Timothy K. Vander Leek, MD, Douglas P. Mack, MD, MSc, Paige G. Wickner, MD, MPH, Alexander G. Singer, MB BAO BCh, David A. Khan, MD, Matthew Greenhawt, MD MBA MSc



PII: S2213-2198(21)00455-4

DOI: <https://doi.org/10.1016/j.jaip.2021.04.015>

Reference: JAIP 3562

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 28 February 2021

Revised Date: 23 March 2021

Accepted Date: 15 April 2021

Please cite this article as: Shaker M, Phillips E, Blumenthal KG, Abrams EM, Banerji A, Oppenheimer J, Vander Leek TK, Mack DP, Wickner PG, Singer AG, Khan DA, Greenhawt M, The importance of a timely second dose of the 2021 COVID-19 mRNA vaccine depends on the protection afforded by a first dose and subsequent risk of anaphylaxis, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.04.015>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

The importance of a timely second dose of the 2021 COVID-19 mRNA vaccine depends on the protection afforded by a first dose and subsequent risk of anaphylaxis

Marcus Shaker MD MSc^{1,2}, Elizabeth Phillips, MD³, Kimberly G. Blumenthal, MD, MSc^{4,5,6}, Elissa M. Abrams, MD⁷, Aleena Banerji, MD⁴, John Oppenheimer, MD⁸, Timothy K. Vander Leek, MD⁹, Douglas P. Mack, MD, MSc¹⁰, Paige G. Wickner, MD, MPH^{5,11}, Alexander G. Singer, MB BAO BCh¹², David A. Khan, MD¹³, Matthew Greenhawt, MD MBA MSc¹⁴

¹Dartmouth-Hitchcock Medical Center, Section of Allergy and Immunology, Lebanon, NH;

²Geisel School of Medicine at Dartmouth, Hanover, NH; ³Department of Medicine, Vanderbilt

University Medical Center, Nashville Tenn; ⁴Division of Rheumatology, Allergy, and

Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Mass;

⁵Harvard Medical School, Boston Mass; ⁶Edward P. Lawrence Center for Quality and Safety,

Massachusetts General Hospital, Boston, Mass; ⁷Department of Pediatrics, Section of Allergy

and Clinical Immunology, University of Manitoba; ⁸Rutgers New Jersey Medical School, Newark,

NJ; ⁹Pediatric Allergy and Asthma, Department of Pediatrics, University of Alberta, Edmonton,

AB; ¹⁰McMaster University, Hamilton, ON, Canada and Halton Pediatric Allergy, Burlington, ON,

Canada; ¹¹Division of Allergy and Immunology, Department of Medicine, Brigham and Women's

Hospital, Boston, Mass; ¹²Department of Family Medicine, University of Manitoba; ¹³Division of

Allergy & Immunology, Department of Internal Medicine, University of Texas Southwestern

Medical Center, Dallas, Texas; ¹⁴Department of Pediatrics, Section of Allergy and Immunology,

Children's Hospital Colorado, University of Colorado Denver School of Medicine

23

24 Word count: 2735

25

26 Corresponding Author: Marcus S. Shaker, MD, MSc, FAAAAI, FACAAI, FAAP, Professor of
27 Pediatrics and of Medicine, Geisel School of Medicine, Dartmouth-Hitchcock Medical Center,
28 Department of Medicine, Section of Allergy and Clinical Immunology, One Medical Center Drive,
29 Lebanon, NH, 03784. 603-653-9885. Marcus.S.Shaker@Dartmouth.edu

30

31 Source of any financial support: None Trial registration: Not applicable

32

33 Key Words: COVID-19; Vaccine; Adverse Effects; Anaphylaxis; Guideline; Shared Decision-
34 Making

35

36 Conflict of interest: MS is a member of the Joint Taskforce on Allergy Practice Parameters; has a
37 family member who is CEO of Altrix Medical; serves on the Editorial Board of the Journal of
38 Food Allergy and the Annals of Allergy, Asthma, and Immunology. EP reports grants from the
39 National Institutes of Health (grant nos. P50GM115305, R01HG010863, R01AI152183,
40 R21AI139021, and U01AI154659) and from the National Health and Medical Research Council
41 of Australia; receives Royalties from Uptodate and consulting fees from Janssen Vertex,
42 Regeneron, and Biocryst; is codirector of IIID Pty Ltd, which holds a patent for HLA-B*57:01
43 testing for abacavir hypersensitivity, and has a patent pending for Detection of Human
44 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. KB has no conflicts to disclose. EA 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, GSK and Sanofi. AB has no conflicts to disclose. JO declares the following:

Research/Adjudication: AZ, GSK, Sanofi, Novartis; Consultant: GSK, AZ, Sanofi; Associate Editor: Annals of Allergy Asthma Immunology, AllergyWatch; Section Editor: Current Opinion of Allergy; Royalties: Up to Date; Board Liaison ABIM for ABAI. TVL has served on advisory boards and received honoraria from Aralez, Bausch Health, and Pfizer. DM 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. He 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. PW has no conflicts to disclose. AS has no conflicts to disclose. DK has no conflicts to disclose. MG 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, Allergenics, 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, the European Academy of Allergy and Clinical Immunology; is an associate

66 editor for the Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Task
67 Force on Allergy Practice Parameters.

68

69 ABSTRACT

70 Vaccination against SARS-CoV-2 represents our greatest hope to combat the devastating
71 COVID-19 pandemic. Amidst ongoing global vaccination efforts, rare cases of severe allergic
72 reactions to COVID-19 mRNA vaccines have received significant attention. Although the exact
73 nature of these reactions may be heterogeneous, various approaches exist to engage with
74 patients, communities, public health departments, primary care providers, and other clinicians
75 in a multidisciplinary approach to advance population health. While it is optimal for patients to
76 receive COVID-19 vaccination as outlined in emergency use authorizations, second dose
77 deferral of mRNA vaccines may be a consideration within a shared decision-making paradigm of
78 care in select circumstances characterized by high durable first vaccine dose protection and
79 significant elevations of vaccine anaphylaxis risk. Still, the durability of protection afforded by a
80 single dose of a COVID-19 mRNA vaccine is uncertain, and alternative approaches to complete
81 vaccination, including precautionary use of a COVID-19 viral vector vaccine, also remain patient
82 preference sensitive options. There is an urgent need to define correlates of COVID-19
83 immunity and the level of longer-term protection afforded by COVID-19 vaccination.

To Second Dose or Not To Second Dose, That is the Question

Within the context of a rapidly mobilizing global vaccination effort to combat COVID-19, questions have emerged regarding whether or not to proceed with a timely second COVID-19 mRNA vaccine dose for individuals who have had a potential allergic reaction to a first dose.(1-4) While guidance has evolved, as of this writing the Centers for Disease Control (CDC) considers a severe allergic reaction after a previous dose of a COVID-19 mRNA vaccine a contraindication to future administration of a COVID-19 mRNA vaccine, and suggests evaluation with an allergist-immunologist for patients with immediate allergic reactions of any severity to an mRNA vaccine.(5) Furthermore, the CDC advises that if delays in administering the second dose are unavoidable, the Pfizer-BioNtech and Moderna COVID-19 mRNA vaccines can be administered up to 6 weeks following the initial dose.(5)

Ultimately, whether to provide or defer a second mRNA vaccine dose in patients at risk for anaphylaxis to a COVID-19 mRNA vaccine warrants an approach grounded in shared decision-making, as this is a highly preference-sensitive care option given current data.(6-8) While the allergist-immunologist engages the patient in shared decision-making, it is important that the clinician guard against a tendency toward risk aversion to “first, do no harm”, particularly given COVID-19 mRNA first-dose effectiveness estimates range from 46% to 93% among various studies with uncertain duration of immunity.(3, 4, 9-14) While the risk of anaphylaxis is real, it is easy to lose sight of the forest for the trees while striving for nonmaleficence through second dose deferral, and actually place a patient at greater risk for disease morbidity in the long term.(15) Furthermore, it is quite possible for the allergist-immunologist to inadvertently

exaggerate the patient's fears and hesitancy in the decision-making process, or even replace a patient's own values with that of the clinician.(8-10) Our specialty has a checkered past in trying to attenuate risk of anaphylaxis in the short term while sacrificing long term health benefits, and we need not look far to find obvious examples, which range from overdiagnosis of anaphylaxis risk to vaccines, foods, and medications.(16-20)

Caveats of Single Dose COVID-19 mRNA Vaccine Immunity

The risk of SARS-CoV-2 infection and its associated morbidity is currently unclear when a single dose of a COVID-19 mRNA vaccine is not followed by the recommended second dose.(1-4, 11-13, 21) Early evidence is encouraging and suggests that a single dose (with certain vaccines) may reduce the risk of symptomatic COVID-19 infection by up to 90%.(3, 4, 21) However, follow-up has been limited for single dose recipients, and this may represent an upper limit of protection that in reality could be much lower.(1-4, 11) The question of whether to delay the second dose of these vaccines to facilitate more rapid dissemination of first vaccine doses has been an area of debate, even in patients without a prior reaction to a first dose.(2) At present, concern remains that deviating from recommended intervals could lead to a suboptimal vaccine immune response.(2) Indeed, we do not yet even know for certain the duration of protection afforded by the full series.(2, 14) Additionally, there should be consideration that the efficacy of a single dose could be comparatively reduced in the elderly and those at risk for high morbidity and mortality associated with COVID-19. Conversely, it is also important to consider that individuals with prior natural SARS-CoV-2 infection might have broader protection

following a single dose.(22) Thus, a decision regarding second dose deferral is challenging since reliable correlates of immune protection and long-term follow-up on outcomes are lacking.

Anaphylaxis-Risk Thresholds for Second Dose COVID-19 mRNA Vaccine Deferral

In weighing the risk versus benefit, could a management strategy consisting of deferral of the second dose of a COVID-19 mRNA vaccine in those with significantly increased anaphylaxis risk be a reasonable option for some? Answering such a question relies on several theoretical assumptions. Decisional modeling is possible if we presume durable immunity lasting at least 12 months from vaccination following a single mRNA vaccine dose and maintain the efficacy rates attributed to the COVID-19 mRNA vaccines from publications supporting emergency use. Adapting a previously published health-economic model of risk-stratification strategies relative to COVID-19 mRNA vaccine anaphylaxis to evaluate anaphylaxis-risk thresholds for deferral of a second dose of these vaccines reveals interesting findings (Table 1).(23) Assuming a very high rate of first dose durable protection of 90% against symptomatic COVID-19 infection over the ensuing year with a 5% additional second dose benefit, deferring a second dose would be cost-effective if anaphylaxis risk exceeds 0.13% (1,300 anaphylaxis cases/million vaccinations; willingness to pay threshold of \$10,000,000 per death prevented). While a 0.13% risk is quite low when considering second dose risk in a patient with a convincing history of anaphylaxis to a first dose, it is well above the currently reported population risk (2.5 to 11.1 anaphylaxis cases per million) for COVID-19 mRNA vaccines.(24, 25) Furthermore, the durability of first (or even second) dose protection is uncertain, and it should be noted that if either the durable immunologic protection of a first vaccine dose falls (an assumption that may be more

realistic),(11) or the overall vaccine efficacy against COVID-19 (and present and future variants in the next year) decreases,(26) the anaphylaxis-risk threshold for second vaccine dose deferral of an mRNA vaccine rises from 0.13% to an upper limit of 6.05-21.72% across estimates of overall vaccine protection (6,005-21,720 anaphylaxis cases/million; Table 1).

While a second-dose deferral trade-off can be calculated, using theoretical assumptions about a durable immune response to the vaccine, it is important to realize that this only reaches thresholds for value-based care at anaphylaxis rates that are far greater relative to reported COVID-19 mRNA vaccination population risk.(24, 25, 27) The science of COVID-19 is currently moving very rapidly, and we are seeing new SARS-CoV-2 variants in the community that are more transmissible and may impact the effectiveness of all COVID-19 vaccines in clinical use or under study that are currently based on a spike protein construct.(26) While estimates can account for variable overall effectiveness against new SARS-CoV-2 variants (Table 1), it remains crucial to realize that cases of true COVID-19 mRNA vaccine anaphylaxis are very rare (24, 25, 28), and the allergist-immunologist is much more likely to encounter patients with non-anaphylactic reactions to mRNA vaccines for which second dose vaccine deferral beyond the accepted 6 weeks would not be in the patient's best interest.

Approaches to Administration of Second Doses of COVID-19 mRNA vaccines

Any analysis of second dose deferral is further limited by the fact that few persons have received a second dose after an initial dose resulted in anaphylaxis, and we do not have accurate estimates for how likely anaphylaxis will recur following a second dose. The CDC

currently advises against second dose or future administration of a COVID-mRNA vaccine for such individuals.(5) However, our experience with other allergies importantly illustrates that reaction severity may not be reproducible, and reactions may not even consistently recur, especially if the mechanism is not IgE-mediated.(29) Graded-dose challenge/desensitization has historically been a cornerstone of management of immediate reactions to vaccines.(29) However, given the novel vaccine platform of COVID-19 mRNA vaccines and their recent clinical use, it must be acknowledged that there is currently no evidence that splitting the dose of mRNA vaccines at any ratio will improve safety, and it could also theoretically negatively affect vaccine efficacy.(6, 7, 29) In addition, there would be no rationale to split the dose or use a graded-dose challenge/desensitization approach in individuals who have had only mild to moderate allergic reactions to the first dose if administration of the second dose of COVID-19 mRNA vaccines as a full single dose (as intended and outlined in the Pfizer-BioNTech and Moderna FDA emergency use authorization (EUA) of these yet to be licensed products) is shown to be safe and well tolerated for such patients. (6, 7, 29) Furthermore, administering COVID-19 mRNA vaccines in accordance with EUA guidance is most likely to result in optimal vaccine efficacy, and allergist-immunologist supervised dosing may pose logistical challenges in accessing, storing, and utilizing vaccine supply in a timely fashion. Still, equipoise in vaccinating groups at both high risk for anaphylaxis and for severe COVID-19 is a delicate balance. As such, for patients at high risk for anaphylaxis to an mRNA vaccine, a graded-dose vaccine challenge/desensitization may be preferable to outright vaccine deferral in the midst of the ongoing pandemic, if the patient and/or clinician would not otherwise proceed with vaccination.(6, 30-32)

Although utilization of another COVID-19 vaccine construct in the setting of a first dose mRNA COVID-19 vaccine is being studied in the UK there is currently no safety, efficacy or effectiveness data for this approach. With the Janssen Biotech COVID-19 vaccine EUA, guidance has been suggested that for patients in whom a second COVID-19 mRNA vaccine dose is contraindicated that this viral vector vaccine may be administered with a precaution under the supervision of a healthcare professional capable of managing anaphylaxis.(33) In this setting, referral to an allergist-immunologist should be considered and the minimum interval for administration after the COVID-19 mRNA vaccine would be 28 days.(33) The Janssen Biotech vaccine is based on a recombinant replication incompetent human adenovirus serotype (Ad26) vector that encodes the SARS-CoV-2 viral spike glycoprotein.(34) At this time the incremental safety and efficacy of administration of the Janssen Biotech vaccine (which contains polysorbate 80 as an excipient) given to an individual who has only received a single COVID-19 mRNA dose is unknown, but represents a patient-preference option to consider if the vaccine is available.(34) However, relying on this approach may have unintended consequences in regard to both population equity (i.e., some patients may receive 1.5 vaccine doses while others receive none) and access in resource constrained settings with limited COVID-19 vaccine supply (i.e, the Janssen Biotech vaccine may not be available to every patient at the time vaccination is needed).

Caveats of Risk Stratification Approaches

Uncertainty presently characterizes many aspects of the COVID-19 vaccines and reactions, which has been further heightened by the emergence of several variants where the amount of protection offered by a single vaccine dose would be even less certain.(1, 26) The benefit of history-guided risk-stratification that may also use excipient skin testing and/or vaccine re-challenge with informed consent and shared decision-making is currently unknown.(6, 7)

Although polyethylene glycol (PEG) is the only excipient in the COVID-19 mRNA vaccines that is shared and can be readily tested, PEG prick and intradermal skin testing has uncertain sensitivity, specificity, and positive and negative predictive values.(6, 7) In addition, getting patients seen and assessed by an allergist-immunologist available to perform this testing within the allowable 6 week time period may be challenging in some areas and could delay vaccination.(6, 7) It is possible that risk-stratification may not be beneficial until the prevalence of vaccine anaphylaxis reaches a much higher threshold than exists in the general population.(6, 7, 23-25) It is still unclear what is triggering reported COVID-19 mRNA vaccine reactions, and through what mechanism they occur. Reactions may be non-IgE-mediated resulting from direct complement or mast cell activation (complement activation-related pseudoallergy, CARPA) which renders it very difficult to predict in whom a second dose reaction may result.(7, 35-39) We can be somewhat reassured that most of the reports of anaphylaxis to date have come from first dose reactions and we are not seeing a more significant signal of anaphylaxis occurring for the first time on the second dose or mild first dose reactions leading to more severe second dose reactions. These and other questions will hopefully be answered as we continue to expand our knowledge base regarding COVID-19 and vaccination related immunity.

236

237 **Opportunities for Shared Decision-Making and Learning**

238 COVID-19 vaccination uncertainties will likely remain a reality of life in 2021 and beyond.

239 Allergists-immunologists must continue to partner with patients and multidisciplinary

240 healthcare providers to discuss the knowns and the unknowns and weigh the benefits and risks

241 of approaches to vaccination. The ultimate goals of optimizing individual and population health

242 outcomes need to be prioritized. As we enter these discussions, we must remember the three

243 conversations of effective shared decision-making – *team talk* to outline patient goals and244 preferences, *option talk* to clarify choices, and *decision talk* to reach preference-based

245 decisions.(8) In this model, an allergist-immunologist's primary role is to provide expert advice

246 regarding the existing evidence (evolving and uncertain as it may be), while acknowledging that

247 patients are the experts of their personal contexts and what matters most to them.(8) This

248 process could be facilitated on a public health level through development of validated patient-

249 decision aids – tools which at present are not available in the context of subsequent dose

250 decisions for patients with prior COVID-19 vaccine reactions.(40) It is highly likely that the vast

251 majority of individuals without prior COVID-19 vaccine anaphylaxis who have concerns about

252 second dose safety can safely receive the second dose , and routinely withholding it would be a

253 disservice not only to their health but also the larger population.(6, 7) Assuming that high

254 durable immunity of a certain threshold can indeed be obtained after a single vaccination, a

255 model of COVID-19 vaccination that considers harms and benefits of deferring or foregoing a

256 second vaccine dose in 2021 could be useful in the individual decision-making paradigm. A

257 shared decision for second dose vaccine deferral might be appropriate in the rare patient with a

greatly elevated relative risk of second dose anaphylaxis where first dose protection is high and there is a low risk of COVID-19 related morbidity (Figure 1). This makes it imperative to determine what constitutes durable first-dose protection of a COVID-19 mRNA vaccine intended to be given as a 2-dose series, as well as to understand the value of the second (or any additional) dose. Vaccination is crucial to ensure both patient and population health – a key consideration as we begin to appreciate the daunting task of fighting a pandemic virus that is actively mutating. Dr. Anthony Fauci noted that “viruses cannot mutate if they cannot replicate”, and so we are in a race against time to pre-empt COVID-19 variants.(41) The dawning realization that COVID-19 is likely to become endemic also necessitates an approach to revaccination of patients with a prior reaction to any COVID-19 vaccine. In the case of the COVID-19 mRNA vaccines, even if a second dose is deferred this year,(1) since annual COVID-19 vaccinations will likely be the norm, decisions will need to be made about future administration of a COVID-19 vaccine even if it is not a COVID-19 mRNA vaccine.(34, 42) Given that multiple additional vaccines will likely be granted EUA in the United States over the next few months,(34) such as the adenoviral vector and protein subunit SARS-CoV-2 vaccines, an additional consideration for the future will be revaccination with a different COVID-19 vaccine construct, although at present such an approach would also be characterized by some degree of uncertainty.

While allergists-immunologists worldwide begin to gain first-hand experience with the clinical assessment and management of individuals who have CDC-defined allergy contraindications or precautions to COVID-19 vaccination, it becomes helpful to have shared platforms for

communicating patient assessments and outcomes. There are notable limitations to the CDC's passive surveillance system for detecting and confirming anaphylaxis. Sharing allergist-immunologist clinical assessment and vaccination outcomes can enrich our clinical knowledge base. Current platforms for clinical data sharing have emerged, including the *COVID-19 Vaccine Allergy Case Registry*,⁽⁴³⁾ a HIPAA-compliant US-based registry for documenting hypersensitivity reactions related to COVID-19 vaccination, developed by the United States Drug Allergy Registry consortium,⁽⁴⁴⁾ and the *Global COVID-19 and Vaccine-Associated Anaphylaxis Surveillance Project*, an international anaphylaxis registry supported by the World Allergy Organization.⁽⁴⁵⁾

Conclusion

As of March 23, 2021, there had been 123,924,888 confirmed COVID-19 cases resulting in 2,727,640 deaths around the world.⁽⁴⁶⁾ Thus far, the risk of anaphylaxis-related death due to COVID-19 immunization appears to be exceptionally rare, with over 458 million doses given to date.^(28, 47, 48) In the months to come the continued emergence of SARS-CoV-2 variants may pose challenges to vaccination strategies.⁽²⁶⁾ There will also be the benefit of additional COVID-19 vaccines being granted EUA in the United States.⁽³⁴⁾ As we continue to provide each patient the right care at the right time, new discoveries will continue to allow insights that will shape and optimize our practice. While we are accumulating this evidence base, our ultimate goal must be to avoid unnecessary vaccine hesitancy and deferral and to optimize both vaccine acceptance and efficacy, while safely vaccinating the world.

References

1. Liu A. How important is the second dose of the COVID-19 mRNA vaccine? *The Journal of Allergy and Clinical immunology in Practice*. 2021.
2. Kadire SR, Wachter RM. Delayed Second Dose versus Standard Regimen for Covid-19 Vaccination. *New England Journal of Medicine*. 2021;<https://www.nejm.org/doi/full/10.1056/NEJMcide2101987>. Accessed February 18, 2021.
3. Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *Lancet*. 2021;<https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2900448-7>.
4. Skowronski DM, De Serres G. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2021;384(11).
5. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States [Available from: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fpfizer%2Fclinical-considerations.html. Accessed February 18, 2021.
6. Greenhawt M, Abrams EM, Oppenheimer J, Vander Leek TK, Mack DP, Singer AG, et al. The COVID-19 Pandemic in 2021: Avoiding Overdiagnosis of Anaphylaxis Risk While Safely Vaccinating the World. *J Allergy Clin Immunol Pract*. 2021.
7. Banerji A, Wickner PG, Saff R, Stone CA, Jr., Robinson LB, Long AA, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. *J Allergy Clin Immunol Pract*. 2020.
8. Abrams EM, Shaker M, Oppenheimer J, Davis RS, Bukstein DA, Greenhawt M. The Challenges and Opportunities for Shared Decision Making Highlighted by COVID-19. *J Allergy Clin Immunol Pract*. 2020.
9. Shaker M, Hsu Blatman K, Abrams EM. Engaging patient partners in state-of-the-art allergy care: Finding balance when discussing risk. *Ann Allergy Asthma Immunol*. 2020;125(3):252-61.
10. Abrams EM, Greenhawt M. Risk Communication During COVID-19. *J Allergy Clin Immunol Pract*. 2020;8(6):1791-4.
11. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021.
12. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-15.
13. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-16.
14. Widge AT, Roupael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. *N Engl J Med*. 2021;384(1):80-2.
15. Abrams EM, Singer AG, Shaker M, Greenhawt M. What the COVID-19 Pandemic Can Teach Us About Resource Stewardship and Quality in Health Care. *J Allergy Clin Immunol Pract*. 2021;9(2):608-12.

16. Shaker M, Stukus D, Chan ES, Fleischer DM, Spergel JM, Greenhawt M. "To screen or not to screen": Comparing the health and economic benefits of early peanut introduction strategies in five countries. *Allergy*. 2018;73(8):1707-14.
17. Abrams EM, Ben-Shoshan M. Delabeling penicillin allergy: Is skin testing required at all? *J Allergy Clin Immunol Pract*. 2019;7(4):1377.
18. Greenhawt M, Turner PJ, Kelso JM. Administration of influenza vaccines to egg allergic recipients: A practice parameter update 2017. *Ann Allergy Asthma Immunol*. 2018;120(1):49-52.
19. Blumenthal KG, Li Y, Banerji A, Yun BJ, Long AA, Walensky RP. The Cost of Penicillin Allergy Evaluation. *J Allergy Clin Immunol Pract*. 2018;6(3):1019-27 e2.
20. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk. *Clin Infect Dis*. 2018;66(3):329-36.
21. Vaccines and Related Biological Products Advisory Committee meeting. December 17, 2020. FDA briefing document: Moderna COVID-19 vaccine [Available from: <https://www.fda.gov/media/144434/download>. Accessed February 23, 2021.
22. Prendecki M, Clark C, Brown J, Cox AL, Gleeson S, Buckian M, et al. Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine. *The Lancet*. 2021;[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)00502-X/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00502-X/fulltext).
23. Shaker M, Abrams EM, Greenhawt M. A Cost-Effectiveness Evaluation of Hospitalizations, Fatalities, and Economic Outcomes Associated With Universal Versus Anaphylaxis Risk-Stratified COVID-19 Vaccination Strategies. *Journal of Allergy and Clinical Immunology In Practice*. 2021.
24. CDC COVID-19 Response Team Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine – United States, December 14-23. *MMWR Morb Mortal Wkly Rep*. 2021;70(2):46-51
25. CDC COVID-19 Response Team Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine – United States, December 21, 2020–January 10, 2021. *MMWR Morb Mortal Wkly Rep*. 2021; 70(4): 125-129.
26. Wu K, Werner AP, Koch M, Choi A, Narayanan E, Steward-Jones GBE, et al. Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine — Preliminary Report. *New England Journal of Medicine*. 2021;<https://www.nejm.org/doi/full/10.1056/NEJMc2102179>.
27. Shaker M, Greenhawt M. A primer on cost-effectiveness in the allergy clinic. *Ann Allergy Asthma Immunol*. 2019;123(2):120-8 e1.
28. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. *Jama*. 2021;325(11):1101-2.
29. Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130(1):25-43.
30. Canadian Society of Allergy and Clinical Immunology Statement of Pfizer/BioNTech Vaccine Anaphylaxis [Available from: <https://csaci.ca/wp-content/uploads/2021/01/COVID-19-VaccineTesting-AdministrationGuidance-JAN5.pdf>. Accessed February 28, 2021.

31. Klimek L, Jutel M, Akdis CA, Bousquet J, Akdis M, Torres-Jaen M, et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines - an EAACI-ARIA position paper. *Allergy*. 2020.
32. Murphy KR, Patel NC, Ein D, Hudelson M, Kodoth S, Marshall GD, Jr., et al. Insights from American College of Allergy, Asthma, and Immunology COVID-19 Vaccine Task Force: Allergic Reactions to mRNA SARS-CoV-2 Vaccines. *Ann Allergy Asthma Immunol*. 2021.
33. ACIP COVID-19 Vaccines Work Group. Clinical Considerations for Use of COVID-19 VAccines. March 1, 2021 [Available from: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/03-COVID-MacNeil.pdf>. Accessed March 1, 2021.
34. FDA US Food and Drug Administration Janssen Biotech Emergency Use Authorization. February 27, 2021 [Available from: <https://www.fda.gov/media/146303/download>. Accessed February 28, 2021.
35. Hamad I, Hunter AC, Szebeni J, Moghimi SM. Poly(ethylene glycol)s generate complement activation products in human serum through increased alternative pathway turnover and a MASP-2-dependent process. *Mol Immunol*. 2008;46(2):225-32.
36. Lund JM, Alexopoulou L, Sato A, Karow M, Adams NC, Gale NW, et al. Recognition of single-stranded RNA viruses by Toll-like receptor 7. *Proceedings of the National Academy of Sciences of the United States of America*. 2004;101(15):5598-603.
37. Kulka M, Alexopoulou L, Flavell RA, Metcalfe DD. Activation of mast cells by double-stranded RNA: evidence for activation through Toll-like receptor 3. *J Allergy Clin Immunol*. 2004;114(1):174-82.
38. Turner PJ, Ansotegui IJ, Campbell DE, Cardona V, Ebisawa M, El-Gamal Y, et al. COVID-19 vaccine-associated anaphylaxis: A statement of the World Allergy Organization Anaphylaxis Committee. *World Allergy Organ J*. 2021;14(2):100517.
39. Szebeni J, Muggia F, Gabizon A, Barenholz Y. Activation of complement by therapeutic liposomes and other lipid excipient-based therapeutic products: prediction and prevention. *Advanced drug delivery reviews*. 2011;63(12):1020-30.
40. International Patient Decision Aid Standards (IPDAS) [Available from: <http://ipdas.ohri.ca>. Accessed March 23, 2021.
41. CNN. Fauci urges vaccinations to stop new virus strains: "viruses cannot mutate if they don't replicate" [Available from: <https://www.cnn.com/2021/02/01/health/us-coronavirus-monday/index.html>. Accessed February 11, 2021.
42. J&J CEO says people may need annual COVID vaccine shots for the next several years [Available from: <https://www.cnn.com/2021/02/09/covid-vaccine-jj-ceo-says-people-may-get-annual-shots-for-the-next-several-years.html>. Accessed February 11, 2021.
43. COVID-19 Vaccine Allergy Case Registry. Mass General Allergy Research [Available from: <https://allergyresearch.massgeneral.org/>. Accessed February 26, 2021.
44. Blumenthal KG, Harkness T, Phillips EJ, Ramsey A, Banerji A, Samarakoon U, et al. Patient Characteristics and Concerns about Drug Allergy: A Report from the United States Drug Allergy Registry. *J Allergy Clin Immunol Pract*. 2020;8(9):2958-67.
45. World Allergy Organization COVID-19 Registry [Available from: <https://www.worldallergy.org/resources/covid-19>. Accessed February 26, 2021.

- 431 46. Johns Hopkins University Coronavirus Resource Center [Available from:
432 <https://coronavirus.jhu.edu>. Access date February 26, 2021.
- 433 47. Coronavirus (COVID-19) Vaccinations [Available from:
434 <https://ourworldindata.org/covid-vaccinations>. Accessed February 11, 2021.
- 435 48. More Than 458 Million Shots Given: Covid-19 Tracker [Available from:
436 <https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/>. Accessed
437 February 11, 2021.
- 438

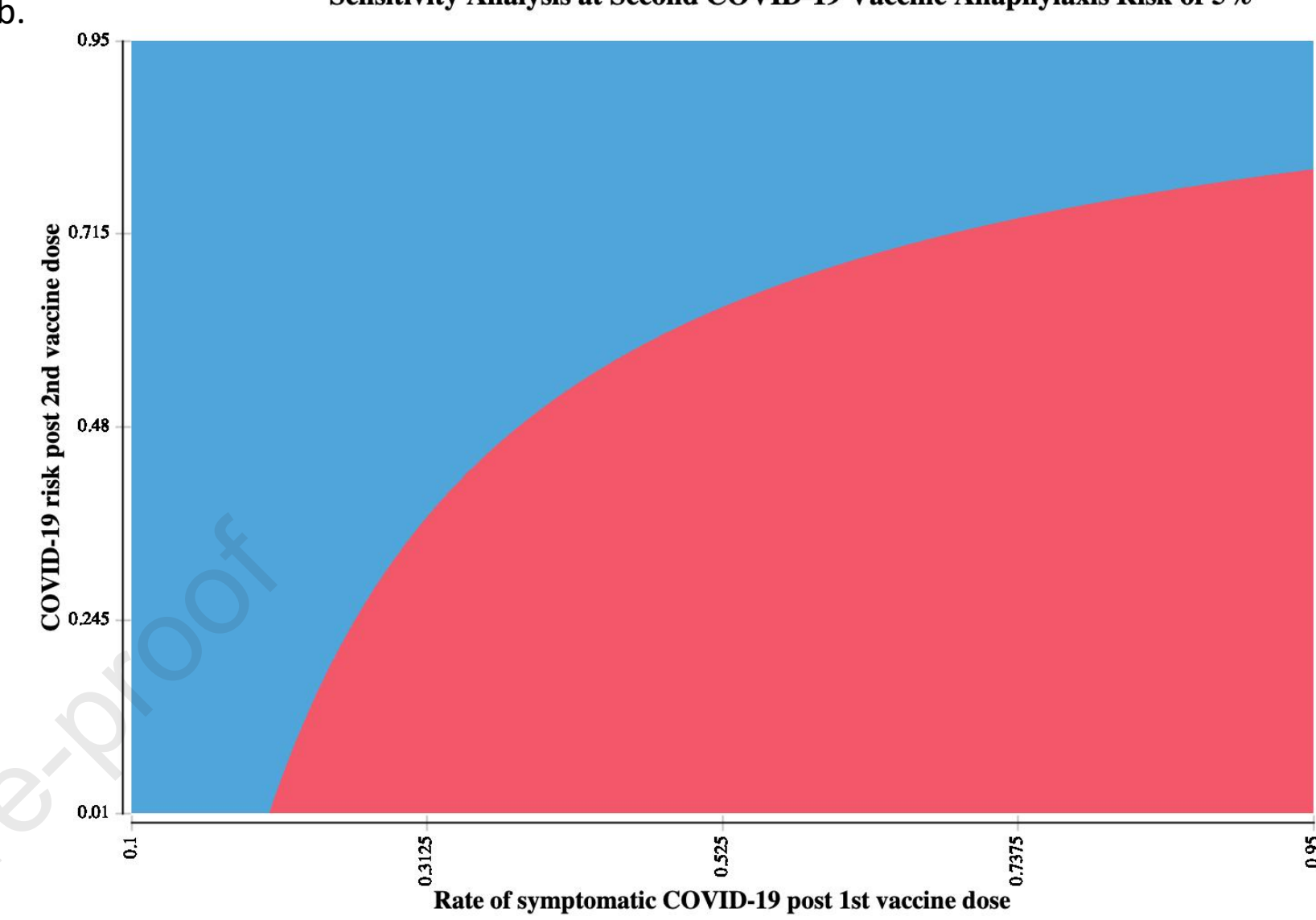
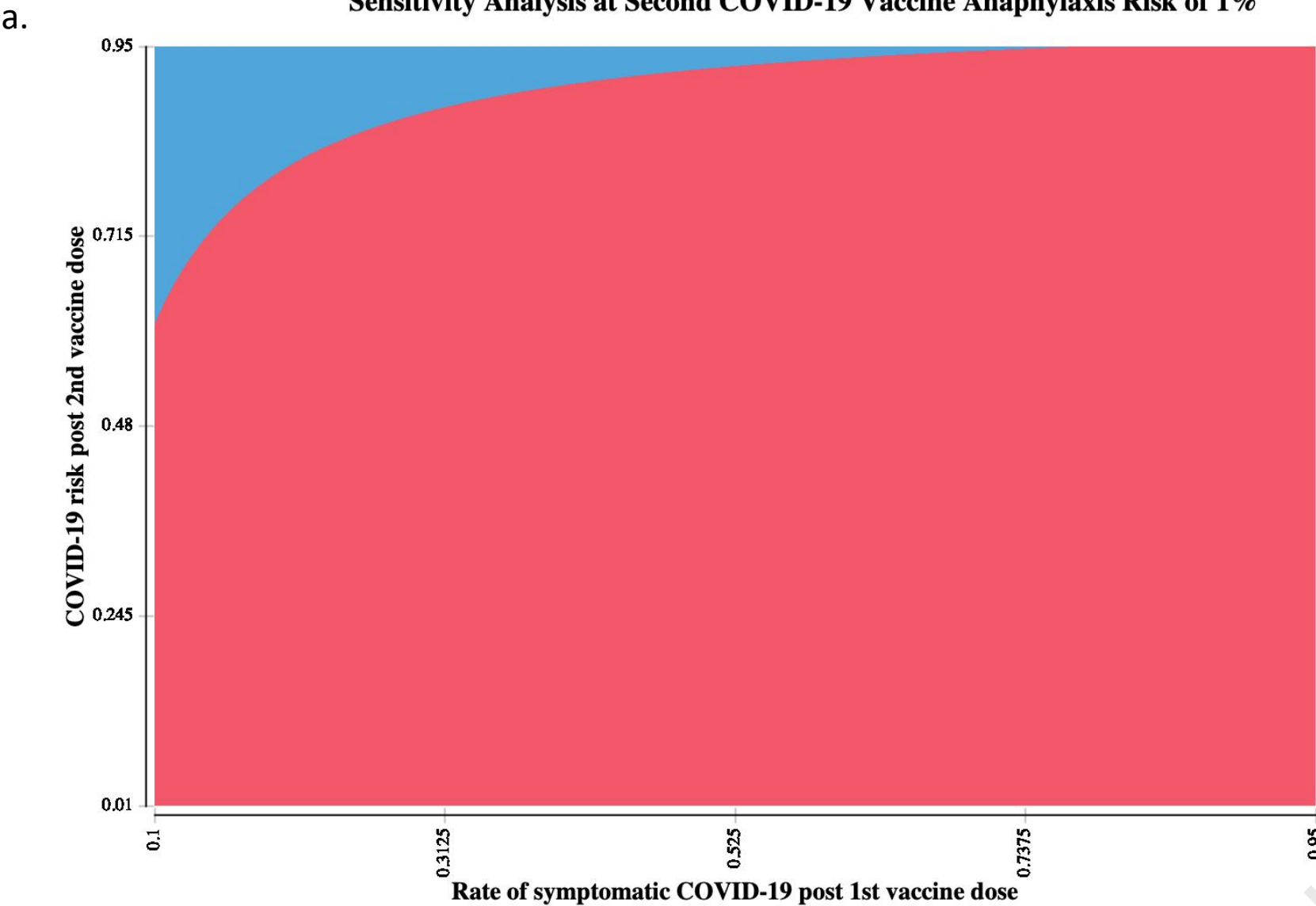
439 **Table 1: Simulation model-based guidance for COVID-19 vaccine second dose deferral.**

<u>First dose protection</u>	<u>Second dose protection</u>	<u>Anaphylaxis risk threshold*</u>
<i>Very high overall vaccine protection</i>		
90%	5%	0.13%
75%	20%	1.27%
50%	45%	5.72%
30%	65%	11.57%
5%	90%	21.72%
<i>High overall vaccine protection</i>		
70%	5%	0.38%
50%	25%	3.18%
30%	45%	8.01%
5%	70%	16.02%
<i>Moderate overall vaccine protection</i>		
45%	5%	0.70%
30%	20%	3.56%
5%	45%	10.88%
<i>Low overall vaccine protection</i>		
25%	5%	0.96%
5%	25%	6.05%

This table demonstrates the anaphylaxis risk threshold projected using different modeled scenarios considering efficacy of the first dose and increase in second dose protection against symptomatic COVID-19 infection. The degree to which first and second dose offer protection to other contacts of the vaccinee was not specifically modeled and could increase the anaphylaxis threshold at which second dose deferral would be cost-effective. *Evaluation of cost-effectiveness threshold (willingness to pay: \$10,000,000 per death prevented) of anaphylaxis risk for a second dose of an mRNA COVID-19 vaccination from a societal perspective. Anaphylaxis risk threshold represents the value at which second vaccine deferral is cost-effective in an at-risk population who has received some degree of durable protection from a first vaccination for the ensuing 12 months.

Figure 1 Title: Cost-effectiveness of 2021 COVID-19 second vaccine dose deferral across anaphylaxis second-dose risk.

Figure 1 Legend: Rates of symptomatic COVID-19 post 1st vaccine dose are shown on the x axis with rates of residual COVID-19 risk after a second dose on the y axis, across rates of 2nd dose vaccine anaphylaxis: 1% (panel a), 5% (panel b), and 15% (panel c).



■ Defer 2nd dose
■ Administer 2nd dose

