# Allergic reactions and adverse events associated with administration of mRNA-based vaccines. A health-care system experience

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## ABSTRACT

**Background:** *Adverse reactions, including anaphylaxis, to messenger RNA coronavirus disease 2019 (COVID-19) vaccines rarely occur. Because of the need to administer a timely second dose in subjects who reported a reaction to their first dose, a panel of health-care professionals developed a safe triage of the employees and health care providers (EHCP) at a large health-care system to consider administration of future dosing.*

**Methods:** *There were 28,544 EHCPs who received their first dose of COVID-19 vaccines between December 15, 2020, and March 8, 2021. The EHCPs self-reported adverse reactions to a centralized COVID-19 command center (CCC). The CCC screened and collected information on the quality of reaction, symptoms, and timing of the onset of the reaction.*

**Results:** *Of 1253 calls to the CCC, 113 were identified as requiring consideration by a panel of three (American Board of Allergy and Immunology) ABAI-certified allergists for future dosing or formal in-person assessment. Of the 113 EHCPs, 94 (83.2%) were recommended to get their second dose. Eighty of 94 received their second planned dose without a severe or immediate reaction. Of the 14 of 113 identified as needing further evaluation, 6 were evaluated by a physician and subsequently received their second dose without a serious adverse reaction. Eight of 14 did not receive their second dose. Only 5 of the 113 EHCPs reported reactions (4.4%) were recommended to not take the second dose: 3 (2.6%) because of symptoms consistent with anaphylaxis, and 2 because of neurologic complications (seizure, stroke).*

**Conclusion:** *The panel demonstrated that, by consideration of reaction history alone, the ECHPs could be appropriately triaged to receive scheduled second dosing of COVID-19 vaccines without delays for in-person evaluation and allergy testing.*

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Coronavirus disease 2019 (COVID-19) is a highly virulent and potentially lethal infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Severe acute respiratory syndrome coronavirus 2 infects populations with cyclical incidence related to laxity of adherence of recommendations to restrict exposure. Vaccination with a lipid nanoparticle–encapsulated, non-replicating, nucleoside-modified messenger RNA (mRNA) based vaccine has an efficacy of >90% against symptomatic and severe disease.[2,3] The employees and health-care providers (EHCP) have a higher risk of acquiring COVID-19,[4] which allowed them to receive the COVID-19 vaccines earlier than other populations.

Severe allergic reactions, including anaphylaxis, have been reported with the two commercially available mRNA-based vaccines: the Pfizer-BioNTech (Manhatten, NY and Mainz, German) COVID-19 vaccine, at a rate of 11.1 reactions per million (0.0011%) vaccine doses administered,[5] and 2.5 reactions per million (0.00025%) for the Moderna (Cambridge, MA) COVID-19 vaccine.[6] Although Blumenthal *et al.*[7] described their prospective experience with employees at Massachusetts General Brigham who received COVID-19 vaccinations and reported allergic reactions to their first doses, no recommendations for a second dose were made. Herein, we describe a process to expedite and safely triage EHCPs who reported adverse reactions to the first dose of the vaccines, followed by a recommendation to administer or refrain from the second dose.

## METHODS

Baylor Scott & White Health (BSWH) is a large not-for-profit health care system in Texas, which includes 52 hospitals and ~42,000 employees.[8] EHCPs were offered the opportunity to be vaccinated with the available vaccine in their region. All EHCPs were advised of potential risks associated with vaccination, and written consent was obtained. EHCPs were screened by asking questions with regard to adverse or allergic reactions to previous vaccinations or medications that contained polyethylene glycol (PEG), polysorbates, and/or polyoxyl 35 castor oil, and were

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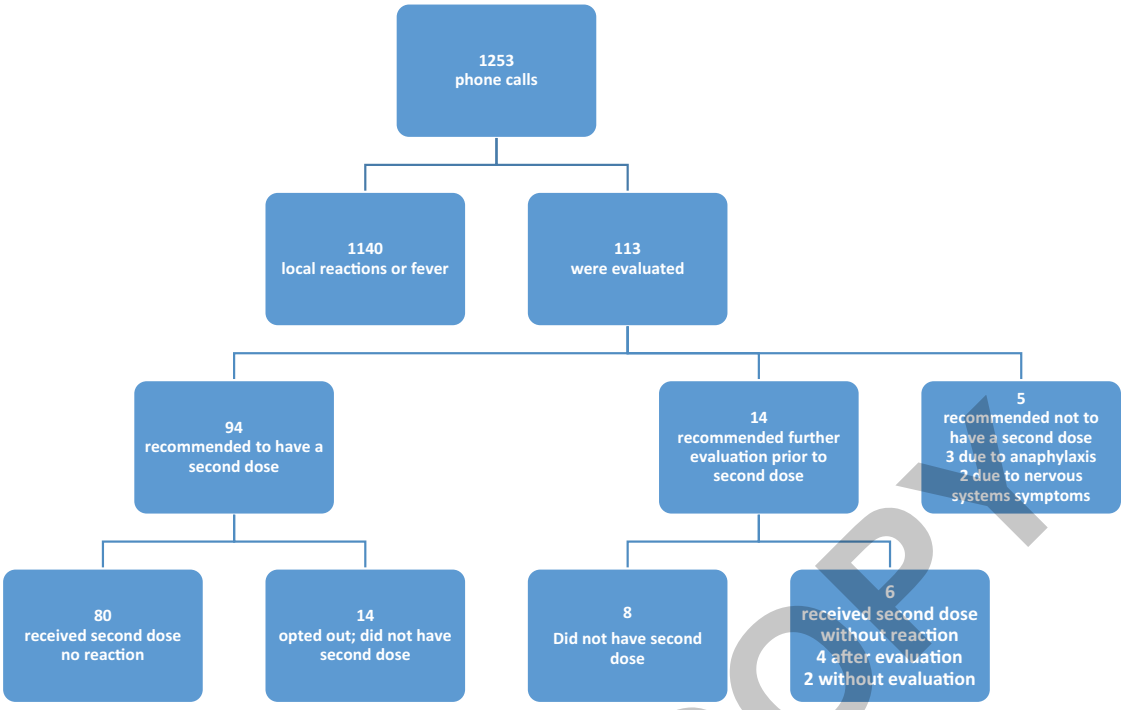


***Figure 1.*** *Algorithm for process used in assessing future risk for second vaccinations.*

advised to defer vaccination if they answered yes. The EHCPs who answered "yes" to this question were excluded from data collection.[9]

BSWH established a COVID-19 command center (CCC) in early 2020 to have a centralized contact for EHCPs with questions about many issues, including exposures, travel, symptoms, testing, and medical leave.[8] Employees from the CCC created and maintained a single data base for monitoring reported adverse events that occurred with EHCPs after the administration of COVID-19 vaccines. The director of the CCC partnered with a panel of three experienced physicians board certified in allergy and immunology (MEA, KD, DW), a director of pharmacy (JT), and occupational nurses (PH) to review each case of an EHCP who reported an adverse event that occurred after immunization. The adjudication of the diagnosis of immediate and severe reactions as defined by the Centers for Disease Control and Prevention, including anaphylaxis, was done by the panel after reviewing standardized information with regard to the reaction concerns.[10–12]

For the purpose of administration of the vaccine, an immediate allergic reaction was defined as a reaction that occurred within 4 hours of administration and included symptoms of hypersensitivity, such as skin rash; pruritus; flushing; hives; feeling of impending doom; swelling of lips, tongue, uvula, and/or throat (angioedema); shortness of breath; wheezing; bronchospasm; stridor; hypoxia; systemic hypotension; tachycardia or syncope; or gastrointestinal symptoms, such as nausea, vomiting, crampy abdominal pain, or diarrhea. Severe allergic reactions were considered if the subject experienced a rapid onset of symptoms consistent with anaphylaxis with acute involvement of at least two systems.[10]

This project was undertaken as a quality-improvement initiative of the BSWH System and, as such, was exempt and not formally supervised by the BSWH Institutional Review Board per its policies on quality-improvement initiatives. The clinical information of the EHCPs reviewed was de-identified in the presentation to the panel who were making clinical recommendations. These clinical recommendations were based on the clinical vignette that was limited to a description of the symptoms, signs, and timing of the reaction in terms of minutes or hours after vaccination. The analysis of the data was limited to descriptive statistics of an observational cohort.

## RESULTS

From December 15, 2020, to March 8, 2021, the total number of doses administered to the EHCPs was 55,039, of which 28,544 were first doses and 26,495 were second doses. During this period, 1253 (4.3% of the EHCPs who received a first dose) called the CCC related to vaccine reactions (Fig. 1). With assistance of the nurses from the CCC, 113 EHCPs (0.39% of the EHCPs who received a first dose of the vaccine) were identified as needing further evaluation by the panel of clinicians for suspected allergic reactions. The median age was 37 years (range, 20–67 years) and most were women (109 [96%]). Of the 113 EHCPs evaluated,

Table 1 **Signs and symptoms of 14 EHCPs recommended for further evaluation***

| Signs and Symptoms | EHCPs, *n* |
|---|---|
| Rash: 5 urticaria, 5 unspecified, 1 maculopapular (*n* = 11) | |
| Men | 2 |
| Women | 9 |
| Respiratory: 2 throat itchy and/or scratchy, 2 throat tightening and/or swelling, 1 short of breath, 1 tongue swelling, 1 wheezing (*n* = 7) | |
| Men | 0 |
| Women | 7 |
| Facial: 2 flushing, 1 numbness and/or tingling lips (*n* = 3) | |
| Men | 1 |
| Women | 2 |

*EHCP = Employees and health-care providers.*
**Multiple symptoms may be present in the same person.*



94 (83.2%) were recommended to take the second dose because the symptoms were consistent with local reactions and with other symptoms, such tiredness, headache, muscle pain, and fever. Eighty of 94 EHCPs (85%) received the second scheduled dose as planned without a severe or immediate allergic reaction and 14 of the 94 (15%) opted not to receive the second scheduled dose.

Of these 113 EHCPs reviewed by the panel, 14 (12.4%) were recommended for further evaluation before receiving the second scheduled dose. Their average age was 39 years (range, 23–61 years). Twelve of the EHCPs were women (86%). The symptoms described by this group were consistent with allergic reactions but were not considered by the panel to be a full contraindication to the second dose. However, these EHCPs needed face-to-face evaluation for in-depth discussion of symptoms (Table 1). Of those, 6 of 14 received the second scheduled dose, 4 after being evaluated by a physician and 2 without further evaluation. None of those six EHCPs who received a second dose had a severe or immediate allergic reaction. The remaining 8 of 14 EHCPs who were recommended further evaluation did not have documentation of receiving a second dose. Only five EHCPs (4.4%) were recommended not to take the second scheduled dose, three of them (0.01% of the EHCPs who received a first dose of the vaccine) were due to anaphylaxis confirmed by emergency department personnel (including one due to anaphylaxis 48 hours after vaccination) and two due to a seizure and a stroke.

## DISCUSSION

The BSWH System reported a cohort of 28,544 EHCPs who received a first dose with either the Pfizer-BioNTech vaccine or the Moderna COVID mRNA vaccine, with 4.3% self-reported adverse events. Only three EHCPs (0.01%) experienced symptoms and signs of anaphylaxis. Extrapolating to similar reports of anaphylaxis between the Pfizer-BioNTech and Moderna vaccines in which 44 anaphylactic reactions (94% were in women) of 9,943,247 doses of the Pfizer-BioNTech vaccine given between December 14, 2020, and January 18, 2021, and 19 anaphylactic reactions (100% women) of 7,581,429 doses of Moderna vaccine,[13] the results of 3 of 28,544 EHCPs seemed greater (105/1,000,000 doses given).

An interesting finding was that the majority of the EHCPs evaluated for reports of potential allergic reactions were women (96%). Although women were a high proportion of health-care workers, the high number represented in this sample was comparable with that noted in other reports.[14,15] In looking at the Vaccine Adverse Event Reporting System (VAERS) data for the same dates as the sample, of 147,349 reported reactions, 115,514 were from women (78%). These results were similar to the analysis by Chen *et al.*[16] of different time points of the VAERS data, which revealed that 80% of the reports were of women. From surveys of initial doses of both vaccines, women were noted to have 87% of nonserious reactions with the Pfizer-BioNTech vaccine[5] and, likewise, 91% of nonserious reactions with the Moderna vaccine.[6]

Vaccine anaphylaxis cases were analyzed by McNeil *et al.*[17] by using the Vaccine Safety Datalink from 2009 through 2011. In their analysis, 33 cases of anaphylaxis (of 25,173,965 doses) from various (non-COVID-19) vaccinations fulfilled the Brighton Collaboration definition.[10] Sixty-one percent were of women, with the majority having anaphylaxis to trivalent influenza vaccines. Of the men cited, the majority reacted to diphtheria, tetanus, and pertussis vaccination.[17] A

Canadian study of anaphylaxis from monovalent AS03-adjuvanted H1N1pdm09 vaccine revealed that, amid 752 reports of allergic symptoms, women accounted for 74% and were 3.9-fold more likely to have anaphylaxis.[18]

In anaphylaxis cases after vaccination with H1N1 pandemic vaccines with Pandemrix (GlaxoSmithKline, London, England) and Arepanrix™ (GlaxoSmithKline, Inc. Mississauga, Ontario, Canada) in 2009–2010, 7.6 per million doses administered were reported to the manufacturer. Of Brighton Class 1–3 (definite certainty), 84% of 97 cases of anaphylaxis were in women.[19] Thus, in comparison with other studies[5,6,16] and current VAERS data,[14,15] the rate of 96% women of those who reported reactions to the mRNA vaccines, although high, is comparable with other studies[17,18] that showed that women are more likely to report adverse reactions and to have anaphylaxis to viral vaccines. An excellent summary for vaccination-triggered anaphylaxis with tables that define the reactions by vaccine can be found in the article by McNeil and DeStefano.[20] For years 2009–2011, anaphylaxis in women was reported in 20 of 13,770,592 doses given (a rate of 1.45 reactions per $10^6$ doses) compared with in 13 of 11,403,373 doses for men (a rate of 1.14 reactions per $10^6$ doses given).

PEG, an excipient of both vaccines to enhance solubility and stabilize the lipid nanoparticle that contains the mRNA, has been found to incite immediate anaphylaxis in many subjects.[9] Based on risk-stratification pathways by Banerji *et al.*,[9] at the time published on the Internet in December 2020, recommendations for the safe administration of mRNA vaccines were instituted and screening questions that assessed the potential for preexisting reactions to excipients in EHCPs were considered.

The panel was able to show that, without PEG testing or the need to physically evaluate the EHCPs who reported adverse effects, allergists were able to effectively review and make recommendations quickly for safe administration of the second dose of the vaccine. Recommendations for prolonged waiting (30 minutes) and formal evaluation by allergists for the EHCPs considered higher risk (based on their first vaccination) allowed successful second-dose vaccinations without significant serious or allergic reactions. This reflected the conclusion of Wolfson *et al.*[21] that skin testing to PEG did not impact the tolerance to the second dose in subjects with immediate or delayed reactions after the first dose of the mRNA vaccines.

Limitations of this study included a retrospective analysis of the data accumulated amid several reporting agencies. Although initial reports were obtained through the CCC, follow up of de-identified information obtained from the records spanned clinics and emergency facilities across the BSWH network in central and north Texas. As a result, consideration of "allergic reaction" versus "anaphylaxis" was left at the discretion of the initial treating physician, who was not an allergist.

However, in the analysis of information of the participants who were affected, the allergists on the panel (MEA, KD, DW) were in agreement with the Brighton Criteria[10] as well as the World Allergy Organization systemic allergic reaction grading system[22] in defining, from the reports, what was anaphylaxis compared with other symptoms, such as itching, rash, hives, globus sensation, or shortness of breath due to hyperventilation. Another limitation was, unlike the study by Blumenthal *et al.*,[7] that no surveys were used to assess symptoms amid all the EHCPs who were vaccinated. Statistical relevance of the frequency of reactions was not addressed in this study except for the predominance of women who reported reactions and the number of anaphylactic and neurologic reactions that prohibited second dosing.

## CONCLUSION

Despite its observational nature, this study represented a "real-world" analysis of the reactions reported by the EHCPs of a major health-care organization. Although anaphylaxis is always a concern with any parenterally administered vaccine, the incidence of anaphylactic reactions to COVID mRNA vaccines is low. Furthermore, the perception of anaphylactic reactions previously reported may have been overreported.[23] This study represents an example of a quality-improvement initiative that exhibited the safety of mRNA COVID-19 vaccinations. The methodology of identification, assessment, and recommendation used without the need for testing provides convenience for patients concerned about the potential for future reactions.



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