



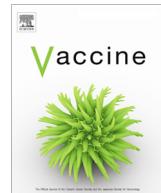
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

Contents lists available at ScienceDirect



Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Relationship between pre-existing allergies and anaphylactic reactions post mRNA COVID-19 vaccine administration

Aditya P. Desai ^a, Aryan P. Desai ^b, Gregory J. Loomis ^{a,*}^a Indiana University School of Medicine, West Lafayette, IN, USA^b Hamilton Southeastern High School, Fishers, IN, USA

ARTICLE INFO

Article history:

Received 15 April 2021

Received in revised form 3 June 2021

Accepted 21 June 2021

Available online 23 June 2021

Keywords:

COVID-19

mRNA vaccine

Anaphylaxis following COVID-19 vaccine

ABSTRACT

Two mRNA vaccines for COVID-19, Pfizer-BioNTech and Moderna, are approved for emergency use in the United States. After their approval and dosing in millions of recipients, reports of anaphylaxis began to appear in the Vaccine Adverse Reporting System (VAERS). Here we provide an analysis of the relationship between prior history of allergy and/or anaphylaxis and anaphylaxis rates following the administration of mRNA COVID-19 vaccines. Overall reported incidence of anaphylaxis was estimated to be rare at 4.2 cases per million doses. It appeared that the *relative* incidence of anaphylaxis following administration of these COVID-19 vaccines was two and seven times higher for recipients with a prior history of allergies and/or anaphylaxis, respectively. This report provides valuable metrics to make evidence-based decisions for subjects with pre-existing allergic conditions receiving a COVID-19 mRNA vaccine.

© 2021 Published by Elsevier Ltd.

1. Introduction

Two mRNA COVID-19 vaccines are currently approved in the United States by Emergency Use Authorization (EUA). The Pfizer-BioNTech mRNA vaccine has been approved since December 11, 2020 by EUA in the United States for individuals 16 years of age and older [1]. The other mRNA vaccine, from Moderna, received EUA on December 18, 2020 for individuals 18 years of age and older [1]. During the clinical trial for the Pfizer-BioNTech COVID-19 mRNA vaccine, the majority of the adverse effects were short-term, mild-to-moderate pain at the injection site, fatigue, and headache [2]. No serious adverse events were specifically attributed to the vaccine group. Similarly, serious adverse events were rare during the clinical assessment of the Moderna COVID-19 mRNA vaccine [3]. The Moderna study reported hypersensitivity reactions in 1.5% of participants in the vaccine group and 1.1% of participants in the placebo group. The study indicated that the ability to detect rare events like hypersensitivity was limited given the vaccine group sample size of 15,210.

Since the EUA for the two mRNA vaccines, as of February 5th, 2021, the Centers for Disease Control and Prevention (CDC) reported that approximately 19.5 million individuals received at least one dose of the Pfizer-BioNTech vaccine and approximately 17 million individuals received at least one dose of the Moderna

vaccine [4]. The CDC conducts passive post-approval vaccine safety monitoring utilizing the Vaccine Adverse Reporting System (VAERS) [5]. The VAERS database relies on spontaneous reporting by recipients and/or healthcare providers of adverse events after vaccination and includes notifications and reports of suspected anaphylaxis. With regards to COVID-19 vaccine related adverse events, reports of anaphylaxis following administration of the two mRNA vaccines began to appear in the VAERS database post EUA [6,7]. Anaphylaxis is an acute life-threatening condition caused by the systemic release of mast cell mediators that can cause asphyxiation and cardiovascular collapse [8]. Most anaphylaxis is IgE-mediated but can also be caused by non-IgE-mediated mast cell degranulation. Some non-IgE-mediated reactions, referred to as anaphylactoid reactions, resemble the clinical presentation of anaphylaxis and respond similarly to epinephrine.

Shimabukuro et al. reported a preliminary analysis of VAERS data for COVID-19 mRNA vaccine-related anaphylaxis [9]. This study was based on nationwide VAERS data as of January 18, 2021, and it reported anaphylaxis rates of 4.7 and 2.5 cases/million doses post Pfizer-BioNTech and Moderna vaccine administration, respectively. In a recent publication by Blumenthal et al., an analysis of acute adverse reactions to mRNA COVID-19 vaccines among the employees of the Mass General Brigham system was reported [10]. In that study, anaphylaxis events following administration of the Pfizer-BioNTech and Moderna vaccines were observed in 0.027% and 0.023% of recipients, respectively and overall incidence rate of anaphylaxis was 2.47 per 10,000 COVID-19 vaccinations.

* Corresponding author at: 715 Clinic Drive, West Lafayette, IN 47907, USA.

E-mail addresses: adidesai@iu.edu (A.P. Desai), gjloomis@iu.edu (G.J. Loomis).

Here, we provide an analysis of relationship between prior history of allergy and/or anaphylaxis and anaphylaxis rates following the administration of mRNA COVID-19 vaccines. Compared to prior reported rates of anaphylaxis following mRNA COVID-19 vaccine administration, this report provides an update based on an additional approximately 19 million doses. Furthermore, we investigated the likely risk of anaphylaxis post mRNA COVID-19 vaccine administration in subjects with pre-existing allergies and anaphylaxis. Our intention is to provide valuable metrics to make evidence-based decisions for subjects with pre-existing allergic conditions receiving a COVID-19 mRNA vaccine.

2. Methods

This analysis was based on VAERS data from 55 states and U.S. territories from December 14, 2020 through February 5, 2021. Adverse reactions to the COVID-19 mRNA vaccines include emesis, fatigue, diarrhea, headache, chills, aches, arm soreness, and fever, among others. The VAERS questionnaire solicits the user to report "Allergies to medications, food, or other products." The examination of the VAERS data revealed allergy reports fitting the above-mentioned criteria and environmental allergens such as pollen, dust, and animal dander among others. Hence, any report which described prior hypersensitivity reactions to these allergens were categorized as having a pre-existing allergic condition. VAERS data captured under recipient "history" and reported "allergy" columns were utilized to identify cases of prior anaphylaxis. Specifically, this was gathered by searching the keywords "anaphylaxis," "anaphylactoid," and fragments of these words followed by manual inspection. Similarly, anaphylaxis following COVID-19 vaccine administration was gathered by searching the abovementioned keywords within the "Symptoms" columns. Anaphylactoid reactions to the COVID-19 vaccine were identified together with anaphylaxis reactions as recommended by the World Allergy Organization [11].

Incidence rates and 95% confidence interval (CI) for each category were calculated using vaccine administrations as the denominator. A χ^2 test with Likelihood Ratio, considering a 2-sided α -value of 0.05 as statistically significant, was also used to compare incidence rates across the vaccine recipient sub-categories shown in Fig. 1. To compare the relationship between age and anaphylaxis following mRNA COVID-19 vaccination among recipients with prior anaphylaxis, a t-Test with α -value of 0.05 was utilized. Analysis was conducted in JMP 15.2.0.

3. Results

There were 12,630 COVID-19 vaccine recipients in the VAERS database with a mean (SD) age of 46 (16) years and 9441 (75%) female recipients. A total of 36,819,212 doses of COVID-19 vaccines were administered, as of February 5 [4]. The overall reported rate of anaphylaxis was 4.2 cases per million doses administered [95% CI: 0.1–8.3]. Of these, anaphylaxis rates of 5.8 [95% CI: 0.98–10.62] and 2.3 [95% CI: –0.73–5.33] cases per million doses were reported for Pfizer-BioNTech and Moderna vaccines, respectively. It should be noted that the following observations were limited to the data reported in VAERS, namely, only among those with reported reactions to the vaccines. Fig. 1 provides a tree-diagram summary of the various subgroups considered in this analysis. The overall reported number of anaphylaxis events within the VAERS dataset was 153 (1.21% [95% CI: 1.02%–1.41%]) cases with similar rates ($P = 0.76$) for the two mRNA vaccines. For the Pfizer-BioNTech vaccine, there were 114 (1.21% [95% CI: 0.99%–1.44%]) reported cases of anaphylaxis while 39 (1.22% [95% CI: 0.83%–1.61%]) cases were reported for the Moderna vaccine. Among the

cases of anaphylaxis following COVID-19 mRNA vaccine administration, no deaths were reported.

Within the VAERS dataset, 4383 recipients reported prior allergic reactions. The reported incidence of anaphylaxis among these recipients compared to those without such history indicated that the former group was twice as likely ($P < 0.0001$) to develop anaphylaxis after receiving the COVID-19 mRNA vaccine. Specifically, a total of 81 (1.85% [95% CI: 1.44%–2.25%]) recipients with prior allergies reported post COVID-19 mRNA vaccine anaphylaxis whereas 72 (0.87% [95% CI: 0.67%–1.08%]) recipients without prior allergies had anaphylaxis.

Among the COVID-19 mRNA vaccine recipients listed in the database, 139 had a prior reported history of allergies and anaphylaxis with a mean (SD) age of 44 (11) years and 129 (93%) females. Among these 139 recipients, 11 recipients reported anaphylaxis following COVID-19 mRNA vaccine administration resulting in an incidence rate of 7.91% [95% CI: 3.33%–12.49%]. Among these 11 recipients, there were eight females and three males. Normalizing for the underlying distribution of sex, females appeared to have a lower incidence of 6.2% compared to males with an incidence rate of 30%, a statistically significant difference ($P = 0.03$). Conversely, among the 12,491 recipients with no prior history of anaphylaxis or allergies, the incidence rate of 1.13% [95% CI: 0.95%–1.33%] for anaphylaxis post COVID-19 mRNA vaccine was significantly lower ($P < 0.0001$) with 142 cases (70 + 72 in Fig. 1). Finally, age did not appear to be significantly associated with anaphylaxis following COVID-19 vaccine administration with a mean (SD) of 44 (11) years for recipients reporting no anaphylaxis and a mean (SD) of 43 (11) years for those reporting anaphylaxis ($P = 0.32$).

4. Discussion

Extending the original retrospective analysis of the VAERS data [9] with a larger dataset inclusive of additional ~19 million COVID-19 vaccine doses, it appeared that anaphylaxis events following vaccine administration remained rare. It appeared that a prior history of allergies and/or anaphylaxis predisposed the recipients to an increased relative incidence of anaphylaxis following administration of the COVID-19 vaccines. These findings emphasize the importance of gathering a thorough history of all potential vaccine recipients especially with a focus on allergic conditions and prior anaphylaxis events. According to current CDC guidelines, vaccination sites should be equipped with at least three doses of epinephrine at all times and have healthcare personnel who are trained and qualified to recognize anaphylaxis and administer intramuscular epinephrine [12]. The guidelines also suggest an additional 15 min of observation (total 30 min) following COVID-19 vaccine administration for individuals with a history of anaphylaxis. The analysis reported here corroborates the CDC recommendations given that an approximately seven times greater incidence rate of anaphylaxis was reported in recipients with prior anaphylaxis compared to those without such history in the VAERS database.

With increased vaccination dosing compared to January, overall reported rate for anaphylaxis from the COVID-19 vaccine remained low (4.2 cases per million doses). Considering the risk of hospitalization and mortality from COVID-19, the benefits of the vaccine far outweigh the low risk of anaphylaxis. These findings provide critical metrics to make evidence-based decisions for subjects with pre-existing allergic conditions receiving a COVID-19 mRNA vaccine.

Limitations of this study include the use of self-reported data and the database does not specify whether a report is submitted by the vaccine recipient or a healthcare provider. In most cases involving anaphylactic reactions, the reports were likely filed by healthcare providers. For this study, it was not possible to utilize

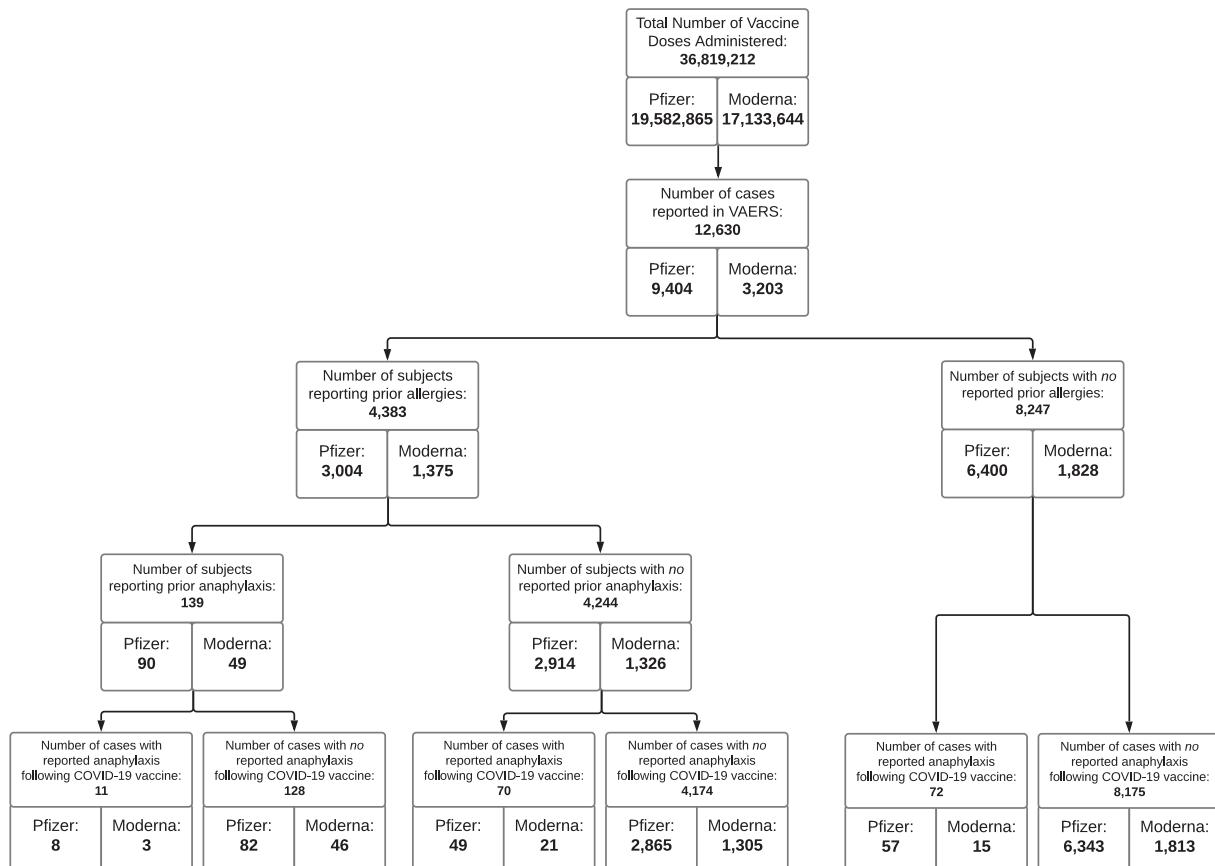


Fig. 1. Summary of data and categories extracted from VAERS database¹ for COVID-19 mRNA Vaccines. (Note: For 23 reports, vaccine manufacturer were not available in the VAERS database).

data from recipients with uneventful outcomes or recipients whose adverse effects were not reported in the VAERS database. As such, the dataset utilized here does not account for the prevalence of allergies and anaphylaxis among the vaccine recipients not present in VAERS. The analysis was based on voluntary data reporting and the study methods may have missed some reporting of prior allergies or anaphylaxis, especially among those who had mild symptoms. At the same time, nationwide spread of the survey with the sample size of 12,630 recipients from 55 states and territories combined with detailed data curation are expected to improve its applicability and reliability.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- CDC. Different COVID-19 Vaccines. Centers for Disease Control and Prevention; 2021. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html> [accessed March 12, 2021].
- 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;383:2603–15. <https://doi.org/10.1056/NEJMoa2034577>.
- 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;384:403–16. <https://doi.org/10.1056/NEJMoa2035389>.
- CDC. COVID Data Tracker. Centers for Disease Control and Prevention; 2020. <https://covid.cdc.gov/covid-data-tracker> [accessed March 13, 2021].
- Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 2015;33:4398–405. <https://doi.org/10.1016/j.vaccine.2015.07.035>.
- 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;70:125–9. <https://doi.org/10.15585/mmwr.mm7004e1>.
- Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. *JAMA* 2021;325:780. <https://doi.org/10.1001/jama.2021.0600>.
- Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. *N Engl J Med* 2021;384:643–9. <https://doi.org/10.1056/NEJMra2035343>.
- 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. <https://doi.org/10.1001/jama.2021.1967>.
- Blumenthal KG, Robinson LB, Camargo CA, Shenoy ES, Banerji A, Landman AB, et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. *JAMA* 2021. <https://doi.org/10.1001/jama.2021.3976>.
- Anaphylaxis vs. Anaphylactoid Reactions | World Allergy Organization; n.d. <https://www.worldallergy.org/ask-the-expert/questions/anaphylaxis-vs-anaphylactoid-reactions> [accessed March 7, 2021].
- Management of Anaphylaxis at COVID-19 Vaccination Sites | CDC 2021. <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html> (accessed March 6, 2021).