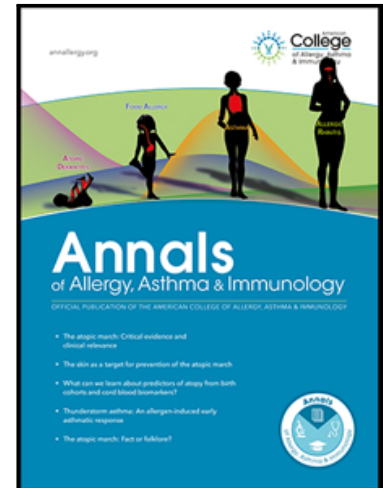


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PII: S1081-1206(21)00267-2
DOI: <https://doi.org/10.1016/j.anai.2021.04.004>
Reference: ANAI 3557



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 5 February 2021
Revised date: 29 March 2021
Accepted date: 1 April 2021

Please cite this article as: Guillermo Rodriguez-Nava MD , Goar Egoryan MD , Daniela Patricia Trelles-Garcia MD , Maria Adriana Yanez-Bello MD , Ricardo Murguia-Fuentes MD , Disproportionality Analysis of Anaphylactic Reactions after Vaccination with mRNA COVID-19 Vaccines in the United States, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.04.004>

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Article type: Letter

Disproportionality Analysis of Anaphylactic Reactions after Vaccination with mRNA COVID-19 Vaccines in the United States

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Funding: The authors declare no sources of funding for this work.

Conflicts of interest: The authors declare no conflicts of interest.

Keywords: COVID-19, vaccine, allergy, anaphylaxis.

Abbreviations: ADR, Adverse Drug Reactions; CDC, Centers for Disease Control and Prevention; CDC WONDER, CDC Wide-ranging Online Data for Epidemiologic Research; COVID-19, Coronavirus Disease 2019; EUA, Emergency Use Authorization; FDA, Food and Drug Administration; PRR, proportional reporting ratio; VAERS, Vaccine Adverse Event Reporting System.

Word count

Main manuscript: 999 words.

Tables: One.

Main manuscript

One year after the emergence of the novel coronavirus SARS-CoV-2 that causes the coronavirus disease 2019 (COVID-19), the United States Food and Drug Administration (FDA) granted two Emergency Use Authorizations (EUA) for two novel mRNA COVID-19 vaccines. Reports of acute hypersensitivity reactions in the real world after EUA are creating anxiety among potential vaccine recipients and may delay achieving universal vaccination (1). Although the Centers for Disease Control and Prevention (CDC) and the FDA jointly monitor vaccine adverse reactions through a variety of surveillance systems such as the Vaccine Adverse Event Reporting System (VAERS) or the CDC's Vaccine Safety Datalink (2), local health care professionals also play an essential role in monitoring vaccine safety, reporting to VAERS, and providing factual and up-to-date information to increase vaccine acceptance.

In a previous report, we have demonstrated the simplicity and versatility of the CDC Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) in conjunction with proportional reporting ratios (PRRs) to obtain up-to-date information about vaccine safety evaluating the reports submitted to the VAERS. No disproportionate reporting of severe adverse drug reactions (ADRs), including anaphylaxis, was found to be associated with the use of the MMR vaccine compared to all other vaccines over 30 years (3). In this report, we used the CDC WONDER Web interface and PRRs to assess whether the number of anaphylaxis cases reported in the VAERS database secondary to the two currently available mRNA COVID-19 vaccines is significantly different from all other vaccines.

We used the CDC WONDER interface to retrieve data from the VAERS national database of all spontaneous ADRs and anaphylaxis reports, including "anaphylactic reaction" or "anaphylactic shock" from the "Symptoms" tab in the site request form, of individuals 18 years of age and older vaccinated with the Pfizer-BioNTech or Moderna vaccines since they were made available to the public in the U.S. and all ADRs and anaphylaxis reports of individuals 18 years of age and older vaccinated with all other vaccines available between December 1, 2020, to March 5, 2021. Unknown and non-mRNA vaccines were excluded. We evaluated disproportionate reporting of anaphylactic reactions relative to all other ADRs after the COVID-19 vaccines compared with all other vaccines using the Evans criteria: $PRR \geq 2$ (where PRR is $a/[a + c]$ divided by $b/[b + d]$ in a 2×2 table), $\chi^2 \geq 4$ with Yates correction (adjustment for low

frequencies), and ≥ 3 individual cases. A disproportionate signal requiring further evaluation is detected if the reports meet all three criteria (4).

A total of 112 368 ADR reports were identified for the mRNA COVID-19 vaccines, and 771 reports for all other vaccines between December 1, 2020, to March 5, 2021, with 185 reports of anaphylaxis for the mRNA COVID-19 vaccines and 1 report of anaphylaxis for all other vaccines over the same time interval. The PPR was 1.26 (95% confidence interval [CI] 0.18 – 9.05), and the χ^2 with Yates correction was 0.043. According to the Evans criteria, a disproportionate reporting of anaphylactic reactions after the COVID-19 vaccines was not found relative to all other vaccines (Table 1).

We found no disproportionate reporting of anaphylactic reactions with the two available mRNA COVID-19 vaccines after EUA was granted. The primary purpose of spontaneous ADRs reporting is to provide early warning of hazards not recognized before marketing an experimental drug because of limitations of clinical trials regarding sample size, duration, and generalizability to real-world practice. In the pivotal phase 3 trials of the mRNA COVID-19 vaccines, participants with a history of severe hypersensitivity reactions to the experimental vaccines or their excipients were excluded. Both trials presented low and similar hypersensitivity-related adverse events in the vaccine and placebo groups (6,7). Following the implementation of vaccination in the real world, reports of anaphylaxis after the first dose of mRNA COVID-19 vaccines emerged. The CDC initially reported 21 case reports submitted to VAERS after administering 1 893 360 first doses of the Pfizer-BioNTech COVID-19 vaccine that met Brighton Collaboration case definition criteria for anaphylaxis and 10 reports after 4 041 396 first doses of the Moderna COVID-19 vaccine, corresponding to an estimated rate of 11.1 cases/million doses administered and 2.5 cases/million doses administered, respectively (2,8). In a recent update, after a total of 9 943 247 doses of the Pfizer-BioNTech vaccine and 7 581 429 doses of the Moderna vaccine, the CDC identified 66 case reports that met the case definition criteria for anaphylaxis: 47 following Pfizer-BioNTech vaccine, for an updated reporting rate of 4.7 cases/million doses administered, and 19 following Moderna vaccine, for a stable reporting rate of 2.5 cases/million doses administered. No deaths from anaphylaxis after vaccination with either vaccine were reported (9). Anaphylaxis after vaccination is indeed a rarely reported event, with an overall reported rate of 1.3 cases/million doses administered for all licensed vaccines (10).

The process of scrutinizing spontaneous ADR data for hazards is known as data mining and signal generation. Browsing the CDC WONDER website and applying PRRs is a relatively simple and straightforward disproportionality analysis method for signal generation based on comparing reporting proportions in a contingency table between the study drug and all drugs in the spontaneous reporting database combined (4,5). However, this method has some significant caveats. First, the VAERS data consist of unverified reports of health events, both minor and severe, that occur after vaccination, and these reports may include incomplete, inaccurate, coincidental, and unverified information. Second, the request form in the CDC WONDER interface only includes broad and non-specific terms for the search engine; hence, some submitted reports may not meet the criteria for anaphylaxis, overestimating the database numbers. Finally, PRRs and Chi-squared values are measures of association, not causality. Establishing causal relationships between vaccines and adverse events requires additional scientific investigation. Ultimately, this method cannot be used for comparative drug safety analysis beyond basic hypothesis generation (5). Despite these limitations, the CDC WONDER interface and calculation of PRRs are a valuable aid to signal generation from spontaneous ADR data that provide clinicians and allergists versatile tools for quick evidence-based decision-making after developing new vaccines and treatments.

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Table

Table 1. PRR calculation of COVID-19 vaccines and anaphylactic reactions

	COVID-19 vaccines	All other vaccines
Anaphylaxis	185	1
All other ADRs	112 183	770
Total	112 368	771

PRR = $a/(a + c)$ divided by $b/(b + d)$ = 1.26, 95% CI 0.18 – 9.05

Chi-squared with Yates correction (1 df) 0.043

Abbreviations: ADR, adverse drug reaction; CI, confidence interval.