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.

Disproportionality analysis of anaphylactic reactions after vaccination with messenger RNA coronavirus disease 2019 vaccines in the United States

One year after the emergence of the novel severe acute respiratory syndrome coronavirus 2 that causes the coronavirus disease 2019 (COVID-19), the US Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for 2 novel messenger RNA (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 revealed 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 evaluating the reports on vaccine safety 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 with all other vaccines in 30 years.[3] In this report, we used the CDC WONDER web interface and PRRs to evaluate whether the rates of anaphylaxis cases reported in the VAERS database secondary to the 2 currently available mRNA COVID-19 vaccines is disproportionately 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 aged 18 years and older vaccinated with the Pfizer-BioNTech (New York City, New York-Germany) or Moderna (Cambridge, Massachusetts) vaccines in the United States between December 1, 2020, and March 5, 2021, and all ADRs and anaphylaxis reports of individuals aged 18 years and older vaccinated with all other vaccines during the same timeframe. 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 greater than or equal to 2 (where PRR is a / [a + c] divided by b / [b + d] in a 2 × 2 table), χ^2 greater than or equal to 4 with Yates correction (adjustment for low frequencies), and greater than or equal to 3 individual cases. A disproportionate signal requiring further evaluation is detected if the reports meet all 3 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, and 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, 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 2 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.[5,6] After 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 per million doses administered and 2.5 cases per million doses administered, respectively.[2,7] 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 after Pfizer-BioNTech vaccine, for an updated reporting rate of 4.7 cases per million doses administered, and 19 after Moderna vaccine, for a stable reporting rate of 2.5 cases per million doses administered. No deaths from anaphylaxis after vaccination with either vaccine were reported.[8] Anaphylaxis after vaccination is indeed a rarely reported event, with an overall reported rate of 1.3 cases per million doses administered for all licensed vaccines.[9]

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.[4,10] 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

Table 1
Proportional Reporting Ratios Calculation of Coronavirus Disease 2019 Vaccines and Anaphylactic Reactions

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

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; COVID-19, coronavirus disease 2019; PRR, proportional reporting ratio.
NOTE. PRR = a / (a + c) divided by b (b + d) = 1.26, 95% CI 0.18-9.05; χ^2 with Yates correction (1 df) 0.043.

Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

interface only includes broad and nonspecific terms for the search engine; hence, some submitted reports may not meet the criteria for anaphylaxis, overestimating the database numbers. Finally, PRRs and χ^2 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.[10] Despite these limitations, the CDC WONDER interface and calculation of PRRs are valuable aids for 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.

Guillermo Rodriguez-Nava, MD*
Goar Egoryan, MD*
Daniela Patricia Trelles-Garcia, MD*
Maria Adriana Yanez-Bello, MD*
Ricardo Murguia-Fuentes, MD†
* *Department of Internal Medicine*
AMITA Health Saint Francis Hospital
Evanston, Illinois
† *Department of Internal Medicine*
Louisiana State University Health Sciences Center
Shreveport, Louisiana

Guillermo.RodriguezNava@amitahealth.org

References

1. de Vrieze J. Pfizer's vaccine raises allergy concerns. Science. 371(6524):10–11.
2. Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. JAMA. 325(8):780–781.
3. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, et al. MMR vaccine adverse drug reactions reports in the CDC WONDER system, 1989-2019. Open Forum Infect Dis. 7(8):ofaa211.
4. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 10(6):483–486.
5. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 384(5):403–416.
6. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 383(27):2603–2615.
7. 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. 70(4):125–129.
8. 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. 325 (11):1101–1102.
9. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. J Allergy Clin Immunol. 143(4):1465–1473.
10. Michel C, Scosyrev E, Petrin M, Schmouder R. Can disproportionality analysis of post-marketing case reports be used for comparison of drug safety profiles? Clin Drug Investig. 37(5):415–422.

Outcome of trimethoprim-sulfamethoxazole challenge in previously reported patients with sulfa antibiotic allergy

Sulfa antibiotics are the drug of choice for treatment and prophylaxis of several infections. Unfortunately, approximately 7% of people exposed to them have adverse reactions ranging from mild rash and nausea to life-threatening reactions, such as Stevens-Johnson syndrome/toxic epidermal necrolysis.[1] Sulfa antibiotics are often avoided in patients with any reported sulfa allergy, irrespective of whether the initial reaction was to an antibiotic or nonantibiotic sulfa drug. This leads to the use of less effective, second-line antibiotics. Desensitization protocols can be used to enable the use of sulfa antibiotics in a patient with a history of reaction to sulfa medications. However, desensitization protocols take hours to days, are expensive, and add logistical hurdles. Desensitization procedures also do not establish tolerance; hence, it must be repeated whenever therapy is required again.

Direct challenge is the gold standard for establishing allergic status or tolerance to medications.[2] One study revealed that 89.3% of patients with a history of immediate, delayed nonsevere, or unknown reactions tolerated direct trimethoprim-sulfamethoxazole (TMP-SMX) oral challenge and 78.8% of the 52 patients who underwent treatment tolerated it.[3] All those who failed the challenge had nonsevere reactions, such as urticaria, skin rash, fever, and pruritus. No individual had any severe immediate or delayed reactions. Another study systematically rechallenged select patients who had adverse reactions to TMP-SMX while undergoing prophylactic therapy and found that 74% of the 27 patients did not have recurrence of their adverse reaction.[4]

With this retrospective cohort study, we reveal the safety of direct oral challenge with TMP-SMX in patients sent to our allergy clinic for evaluation of a reported sulfa allergy. We include a cohort of patients who were undergoing stem cell transplant for hematological malignancies.

This study was completed with approval from the University of Washington Medical Center (UWMC) institutional review board (STUDY00010440). Patients were identified by the UW Medicine Enterprise Data Warehouse and pharmacy records. Research Electronic Data Capture was used for standardized data collection.[5] All patients seen in the UWMC allergy and immunology clinic from June 2017 to May 2020, had a reported sulfa allergy, and underwent the TMX-SMP challenge were included. Patients were excluded if they did not undergo a challenge. Manual chart review was done to abstract patient characteristics (age, sex, race, relevant comorbidities, reported sulfa allergy, types of reaction, and other allergies), reasons for referral (need for prophylaxis, infection in which there was lack of alternative antibiotics, anticipated need for sulfa use, or multidrug allergy), and type of challenge (1 dose, 2 doses, or 3 doses). Challenge outcome was determined by reviewing notes from the challenge encounter and after 3 days. Subsequent TMP-SMX use and comfort with potential use after challenge was determined by manual chart review and calling patients. Data were summarized with descriptive statistics.

From June 2017 to May 2020, a total of 37 patients underwent direct oral challenge. There were 3 patients who reported allergies to nonantibiotic sulfas, and they were excluded from further analysis. The remaining 34 patients are described in Table 1. Most of our patients were of female sex (26/76.5%) and White (28/82.4%).

Ms Benesch and Dr Atluri contributed equally to this work.

Disclosures: The authors have no conflicts of interest to report.
Funding: Dr Atluri is supported by the Host Defense Training in Allergy and Infectious Diseases T32 (5T32AI007044-45). Use of Research Electronic Data Capture is supported by Institute of Translational Health Science grant support from the *National Center for Advancing Translational Sciences*/National Institutes of Health (UL1 TR002319, KL2 TR002317, and TL1 TR002318).