VAERS-reported new-onset seizures following use of COVID-19 vaccinations as compared to influenza vaccinations

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The incidence of new-onset seizures, which we defined as de novo seizures occurring within 4 weeks of receiving any of the US Food and Drug Administration-approved COVID-19 vaccinations as reported in patient-reported data compiled in the US Centers for Disease Control and Prevention Vaccine Adverse Events Reporting System Data (CDC VAERS), has not been explored. The VAERS database contains de-identified patient-reported adverse events following vaccination and represents post-marketing surveillance and analysis of vaccine safety. After adjusting for time at risk, this resulted in estimated incidence rates of 3.19 seizures per 100,000 persons per year for the COVID-19 vaccine and 0.090 seizures per 100,000 persons per year for the influenza vaccines. A data-driven, individualized dataset that is comprehensive and coupled with a longitudinal follow-up in larger numbers of vaccinated individuals is needed to expand on our preliminary findings of vaccine-related seizures.

KEYWORDS
COVID-19, influenza vaccine, Johnson and Johnson vaccine, Moderna vaccine, Pfizer vaccine, seizures, VAERS data

1 | INTRODUCTION

In general, Vaccine Adverse Events Reporting System (VAERS) is a database that receives reports of adverse events and reactions that occur following vaccination administration. The sources for VAERS data are derived from healthcare providers, vaccine manufacturers and the public. While very important in monitoring vaccine safety, VAERS reports alone cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. Some of the disadvantages of VAERS data include reports that are incomplete, inaccurate, coincidental or unverifiable. Most reports to VAERS are voluntary, which means they are subject to biases. This creates specific limitations on how the data can be used scientifically. Hence, data from VAERS reports must be interpreted with these limitations in mind. We undertook this study of VAERS and COVID 19 vaccines since there has been very limited information, if any, on de novo seizures following vaccination administration.

2 | METHODS

This study was performed using publicly available datasets; no Institutional Review Board approval was required.

We compiled the incidence of new-onset seizures among those who received the Pfizer, Moderna or Janssen vaccines and compared the data to influenza vaccines as a reference. For this study we extracted and consolidated vaccine data in adults (age range 18–90 years) from August 2018 to March 2021 from the VAERS database for influenza-related events and between December 15, 2020 to May 13, 2021, for the COVID-19 vaccines, using a custom-designed dataset that is comprehensive and coupled with a longitudinal follow-up in larger numbers of vaccinated individuals is needed to expand on our preliminary findings of vaccine-related seizures.

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software program written in Python. We identified patients who self-reported seizures within the first 4 weeks of receiving the vaccine(s) and compiled the incidence of new-onset seizures among those who received the Pfizer, Moderna or Janssen vaccines; the control group consisted of those who received influenza vaccines. The 4-week cut-off following vaccination was arbitrarily chosen as there are no specific guidelines to follow.

To calculate incidence rates, time at risk for COVID-19 vaccine patients was estimated using freely available daily vaccine data from VAERS. Daily influenza vaccination data were unavailable, therefore time at risk for the influenza vaccine patients was calculated assuming that the total number of individuals receiving a vaccine during an influenza season was uniformly distributed over the days. An influenza season was defined as starting on August 1 and extending to March 1 of the following year. Data was collected from a self-reported publicly available database.

To assess the potential for differential reporting, we additionally looked at the incidence rates of two commonly reported side effects: headaches and injection-site reactions such as pain/rash/swelling.

3 | RESULTS

Between December 15, 2020, and May 13, 2021, a total of 277,209 338 COVID-19 vaccines were administered in the United States. During the 2018, 2019 and 2020 influenza seasons a total of 155.3 million, 174.5 million and 189.4 million influenza vaccines were administered, respectively. During those time periods, 1408 individuals receiving the COVID-19 vaccine and 140 individuals receiving the influenza vaccine reported a seizure-related event. Table 1 lists the demographic characteristics by vaccine type for individuals experiencing seizures. After adjusting for time at risk, this resulted in estimated incidence rates of 3.19 seizures per 100,000 persons per year for the COVID-19 vaccine and 0.090 seizures per 100,000 persons per year for the influenza vaccines. This represents a 35.4-fold increase in seizure rates for the COVID-19 vaccine compared to the influenza vaccines. The demographic characteristics of seizure patients and seizure incidence rates for individuals who took the influenza and COVID-19 vaccines are shown in Table 1.

Tables 2 and 3 show the demographic and incidence rates of the side effects of injection-site reactions and headaches, respectively. For individuals receiving a COVID-19 vaccination, the incidence rate for injection site reaction was 52.3 times higher than those receiving an influenza vaccination and showed the incidence of headache was 92.1 times higher for those who received the COVID-19 vaccine compared to those who received the influenza vaccines.

4 | DISCUSSION

Monitoring for seizures as an adverse event in post-licensure vaccine safety contributes to the robustness of the safety monitoring of the US influenza immunization program but the VAERS database primarily relies on patient-reported numbers.

On December 14, 2020, the US Food and Drug Administration (FDA) issued the first emergency use authorization (EUA) for the COVID-19 vaccine submitted by Pfizer Inc. in partnership with BioNTech Manufacturing GmbH. The mRNA vaccine, BNT162b2, is given as two intramuscular (IM) injections, 0.3 mL each, 3 weeks apart for prevention of COVID-19 in individuals 16 years or older. On December 18, the FDA approved EUA for a second vaccine, Moderna, also an mRNA vaccine, for individuals 18 years or older, which is given IM as a series of two doses, 0.5 mL each, 1 month apart for COVID-19 prevention. A third vaccine, based on a viral vector and manufactured by Johnson and Johnson (J&J), was FDA-approved on February 27, 2021, for EUA use in those 18 years or older as a single IM dose of 0.5 mL for prevention of COVID-19 disease. Healthcare providers (HCP) are required by law to report any adverse events following COVID-19 vaccination or vaccine administration errors to VAERS.

In this analysis, the incidence of new-onset seizures following COVID-19 vaccines was 3.191, as compared to 0.090 for influenza vaccines, representing a 35.4 increase. Most seizures for either group occurred within about 2 days following the vaccination. The higher associated incidence among those vaccinated against COVID-19 is not an endorsement that one group of vaccines is safer or
worse than the other. The VAERS data has facilitated research in vaccine safety at a national level and gives the FDA and CDC an early warning system to monitor side effects from vaccination. It is recognized that VAERS reports may include incomplete, inaccurate, coincidental and unverified information, which is a major drawback. The incidence of new-onset seizures following COVID-19 vaccinations is not from the Weber effect, a phenomenon described as peaking of adverse effects at the end of 24 months, since our study period was <6 months. However, confounding limits the scope of our findings.

To evaluate the potential effect of differential reporting, we additionally analysed the incidence of two commonly reported side effects: headache and injection-site reactions (pain, rash, swelling). We found incidences of 92.1 and 52.3 times higher for COVID-19 vaccines compared to influenza vaccines for headache and injection-site reactions, respectively.

**TABLE 1** Demographic characteristics of seizure patients and seizure incidence rates for individuals who took the influenza and COVID-19 vaccines

| Influenza (n = 142) | Overall (n = 1408) | Janssen (n = 347) | Moderna (n = 525) | Pfizer (n = 536) |
|---------------------|-------------------|-----------------|------------------|-----------------|
| Age, years (SD)     | 44.5 (21.3)       | 46.4 (19.1)     | 37.7 (15.6)      | 49.5 (19.3)     | 49.0 (19.3)     |
| Sex                 |                   |                 |                  |                 |                 |
| Male                | 67 (47.2%)        | 816 (57.9%)     | 179 (51.6%)      | 205 (39.1%)     | 208 (38.8%)     |
| Female              | 75 (52.8%)        | 592 (42.1%)     | 168 (48.4%)      | 320 (60.9%)     | 328 (61.2%)     |
| Days until onset, mean (SD); median (range) | 1.1 (2.8); 0 (0–18) | 1.9 (4.5); 0 (0–28) | 1.5 (4.2); 0 (0–28) | 2.1 (4.8); 0 (0–28) | 1.9 (4.2); 0 (0–26) |
| Incidence rate per 100 000 per year<sup>a</sup> | 0.090             | 3.191           |                  |                 |                 |

<sup>a</sup>Calculated based on time at risk for the rates of vaccination shown.

Influenza:
2018–2019 season: 155.3 million.
2019–2020 season: 174.5 million.
2020–2021 season: 189.4 million.
COVID-19:
12/15/2020–5/13/2021: 277.2 million.

**TABLE 2** Demographic characteristics and injection site reaction incidence rates for individuals who took the influenza and COVID-19 vaccines, any onset

| Influenza (n = 368) | Overall (n = 5280) | Janssen (n = 93) | Moderna (n = 4768) | Pfizer (n = 419) |
|---------------------|-------------------|-----------------|------------------|-----------------|
| Age, years (SD)     | 58.8 (15.1)       | 51.1 (16.5)     | 44.1 (13.5)      | 51.5 (16.5)     | 48.8 (16.6)     |
| Sex                 |                   |                 |                  |                 |                 |
| Male                | 81 (21.9%)        | 546 (10.3%)     | 18 (19.4%)       | 467 (9.8%)      | 61 (14.6%)      |
| Female              | 289 (78.1%)       | 4734 (89.7%)    | 75 (80.6%)       | 4301 (90.2%)    | 358 (85.4%)     |
| Days until onset, mean (SD); median (range) | 1.2 (2.0); 1 (0–18) | 5.8 (4.1); 7 (0–28) | 1.9 (2.9); 1 (0–14) | 6.2 (4.0); 7 (0–28) | 2.5 (3.9); 1 (0–27) |
| Incidence rate per 100 000 per year<sup>a</sup> | 0.238             | 11.965          |                  |                 |                 |

<sup>a</sup>Calculated based on time at risk for the rates of vaccination shown.

Influenza:
2018–2019 season: 155.3 million.
2019–2020 season: 174.5 million.
2020–2021 season: 189.4 million.
COVID-19:
12/15/2020–5/13/2021: 277.2 million.
transient effects of the vaccination. Another study noted that adverse events following COVID-19 vaccinations were generally non-severe in nature.5 According to the website https://www.epilepsy.com/learn/covid-19-and-epilepsy/covid-19-vaccination, there is no evidence that persons with epilepsy are at higher risk of side effects after vaccination and it is generally accepted that there is no causal link between vaccination and seizures.6 This is critical information to consider given that most patients with new-onset seizures are evaluated by emergency room physicians or physician extenders as well as primary care providers.

Our results need to be interpreted with caution since reporting of the adverse effects for COVID-19 vaccines have garnered increased attention by the health authorities, HCPs and patients themselves probably because the vaccines evolved under EUA during the COVID-19 pandemic and not related to the phenomenon of Weber effect. Our findings are not intended for comparison between vaccine safety questions.

We surmise that the increased incidence of seizures, headaches and injection-site reactions among recipients of the COVID-19 vaccines compared to influenza vaccines could be the result of increased reporting/awareness among vaccinees at a time of global pandemic caused by the SARS-CoV2 virus. It must be realized that side effects are associations; the increased side effects of the newer vaccines are probably magnified given the miniscule side effect profile of influenza vaccines. Additionally, VAERS data lack contextual information and could be biased because reporting is voluntary. Lastly, none of the side effects we reported typically require hospitalization and are generally self-limiting. VAERS is an open-access system and data reporting is not prescreened by statisticians or data analysts before being posted and therefore caution must be exercised so as not to overinterpret our results. The advantages of VAERS is that while it is a passive surveillance system it allows health authorities to detect safety issues that can be dangerous, rare and therefore be a foundation for further studies.

COMPETING INTERESTS
The authors declare no conflict of interest with any of the products listed in the study.

AUTHOR CONTRIBUTION
J.A.: concept, design, data analysis and manuscript write-up. C.McL.: statistical analysis and data presentation. L.P.: data curation/presentation and analysis. S.M. and S.Q.: seizure phenomenology. P.Z.: data analysis, expert opinion on vaccines and manuscript preparation.

DATA AVAILABILITY STATEMENT
Data are available upon request as per the guidelines of the journal. VAERS is a publicly available dataset that is accessible to all those interested in data extraction and analysis.

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TABLE 3  Demographic characteristics and headache incidence rates for individuals who took the influenza and COVID-19 vaccines, any onset

|                | Influenza | Overall | Janssen | Moderna | Pfizer |
|----------------|-----------|---------|---------|---------|---------|
| (n = 1583)     |           | (n = 41346) | (n = 6909) | (n = 18852) | (n = 15585) |
| Age, years (SD) | 56.1 (15.0) | 48.0 (15.1) | 43.6 (13.7) | 49.9 (15.4) | 47.6 (15.0) |
| Sex            |           |         |         |         |         |
| Male           | 365 (23.1%) | 8197 (19.8%) | 1724 (35.0%) | 3685 (19.6%) | 2788 (17.9%) |
| Female         | 1218 (76.9%) | 33149 (80.2%) | 5185 (75.0%) | 15167 (80.4%) | 12797 (82.1%) |
| Days until onset, mean (SD); median (range) | 0.8 (1.6); 0 (0–14) | 1.4 (3.2); 1 (0–28) | 1.5 (3.6); 0 (0–28) | 1.4 (3.2); 1 (0–28) | 1.3 (3.0); 1 (0–28) |
| Incidence rate per 100 000 per year* | 1.017 | 93.696 |

*Calculated based on time at risk for the rates of vaccination shown.
Influenza:
2018–2019 season: 155.3 million.
2019–2020 season: 174.5 million.
2020–2021 season: 189.4 million.
COVID-19:
12/15/2020–5/13/2021: 277.2 million.
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