Comparison of adverse events between COVID-19 and Flu vaccines

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Abstract

BACKGROUND: Among the various driving factors for vaccine hesitancy, confidence in the safety associated with the vaccine constitutes as one of the key factors.

OBJECTIVES: This study aimed to explore and compare the adverse events of COVID-19 and Flu vaccines among persons who reported having adverse event on at least the first dose of receiving any COVID-19 or Flu vaccine as reported to VAERS database.

DESIGN: We used a descriptive study design. We selected VAERS records based on our selection criteria to perform descriptive data analysis with relative risk and associated 95% confidence intervals.

SETTING: Adverse events reports from various US territories as obtained from the VAERS database was used.

PARTICIPANTS: The participants were selected from the VAERS data from 01/01/2020 to 08/20/2021 who were greater than 12 years old and received any of COVID-19 or Flu vaccines. Participants with mixture of COVID-19 vaccines, missing age data, missing first dose COVID-19 vaccine information were excluded.

RESULTS: Various common adverse events between Flu and COVID-19 vaccines have been identified. Adverse events such as headache and fever were very common across all age-groups and vaccine groups. Our study also quantified the proportion of rare adverse events such as Guillain Barre Syndrome and Gynecological changes in the VAERS database for COVID-19 vaccines.

CONCLUSIONS: Based on the available data and results, it appears that there were some common adverse events between Flu vaccines and COVID-19 vaccines. These identified common adverse events warrant further investigations based on the relative risk and 95% CI.

Keywords: coronavirus; COVID; COVID-19; Flu; Influenza; vaccine; side effects; adverse events; adverse effect; age group; Pfizer; Moderna; Janssen; Guillain Barre Syndrome; Gynecological changes

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated condition coronavirus disease 2019 (COVID-19), are at the center of the largest public health crisis in over a century. As of January 2022, it has infected over 326 million people and resulted in over 5.5 million deaths worldwide[1].

Considering the serious public health risk posed by the virus, the United States Food and Drug Administration (FDA) issued three Emergency Use Authorizations for COVID-19 vaccines. Since December 11, 2020 various COVID-19 vaccines have been authorized for prevention of COVID-19 by FDA [2–4]. COVID-19 vaccines use newer technologies like mRNA and updated vector-borne vaccine protocols. Despite phase 3 studies demonstrating their safety[5,6], people are skeptical about their efficacy and the frequency and severity of adverse events (AEs). In comparison, yearly influenza (flu) vaccinations have been given for more than 75 years, and their safety is generally accepted. Under such circumstances, it is natural for the public and clinicians to compare the safety profiles, including AEs, between COVID-19 and flu vaccines. Several studies are currently being conducted to monitor the AEs of COVID-19 vaccines prospectively[7–9]. Based on our literature review, this is the first study that compares the three popular COVID-19 vaccines ((BNT162b2)Pfizer[5], (mRNA-1273)Moderna[6], and

(Ad26.COV2.S) Janssen[10]) available in the United States with flu vaccine AEs using a descriptive study design with the Vaccine Adverse Effect Reporting System (VAERS) database.

This study aimed to explore and compare AEs of COVID-19 and flu vaccines among persons who reported having an AE after receiving their first dose of either immunization, as reported in the VAERS database. Among those top 10 common AEs, relative risks (RR) and associated 95% confidence intervals were calculated. By comparing the RR of the top 10 most common AEs between publicly trusted flu vaccines and COVID-19 vaccines, we expect that these measures of association will help address the evidence gap in communicating the risks associated with COVID-19 vaccination. This comparison attempts to overcome one of the components of vaccine hesitancy.

Methods

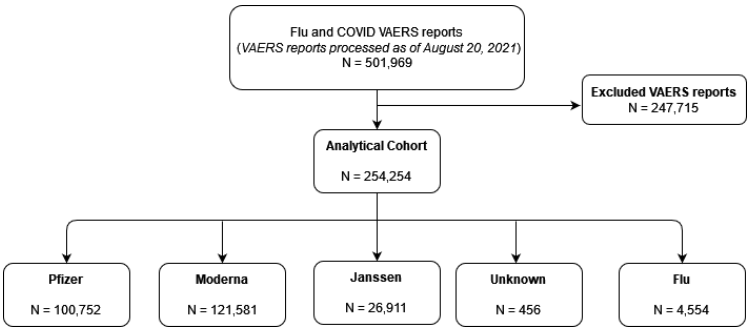
Data source

VAERS is a passive national surveillance system administered by the Centers for Disease Control (CDC), the FDA, and other agencies of the U.S. Department of Health and Human Services (HHS) [11]. The VAERS database can help identify event patterns that may indicate potential safety issues, which can lead to further detailed investigation. Health care providers and vaccine manufacturers have certain obligations to report at least a subset, if not all of the AEs that they become aware of to VAERS. However, VAERS reports may be submitted by anyone involved with the vaccination, including patients, parents, vaccine manufacturers, and many others, regardless of plausibility. Thus, some modifications over time have made VAERS stronger and more flexible to handle stringent selection criteria. Reported AEs are coded into VAERS using the Medical Dictionary for Regulatory Activities (MedDRA) [12]. Because our study used de-identified data from a publicly available health surveillance system, IRB review was not required.

Study Design, Participants, and Setting

VAERS data from 01/01/2020 to 08/20/2021 were used for this descriptive study. Reports from U.S. territories were included if they met all the study criteria. Additional eligibility criteria included being 12 years or older and an indication of either COVID-19 or flu vaccination in the data. Flu vaccine types included in the study were: trivalent(FLU3), quadrivalent(FLU4), Trivalent, adjuvantFLUA3, Quadrivalent, adjuvant(FLUA4), Trivalent, cell-culture-derived(FLUC3), Quadrivalent, cell-culture-derived(FLUC4), Quadrivalent(Nasal Spray)(FLUN4), Trivalent, Recombinant(FLUR3), Quadrivalent, Recombinant (FLUR4), Unknown Manufacturer(FLUX), Monovalent, Unknown manufacturer(FLUX(H1N1)), Monovalent(FLU(H1N1)). Flu vaccine manufacturers included: CSL Limited, GlaxoSmithKline Biologicals, Medeva Pharma LTD, MedImmune Vaccine Inc., Novartis Vaccines and Diagnostics, Protein Sciences Corporation, Sanofi Pasteur, Seqirus Inc., and "unknown." COVID-19 vaccine types included in the study were mRNA and viral vector vaccines. COVID-19 vaccine manufacturers included: Pfizer, Janssen (known publicly as "Johnson & Johnson"), Moderna, and "unknown." Records were excluded if they were missing age data, did not include a manufacturer of the first vaccine dose (i.e., cases where manufacturer information was only available on the second dose of the vaccine), or indicated use of COVID-19 vaccines from two different manufacturers (e.g., cases where a person received Moderna for their first dose and Pfizer for their second dose). A study flow diagram illustrating cohort sizes is shown in Figure 1.

Figure 1: Study Flow diagram representing the cohort



Data Preprocessing and Outcomes

We removed VAERS reports that reported AEs with more than one type of vaccine during the study period. This ensured that AEs from reports that used two different COVID-19 vaccines (e.g., Moderna and Pfizer) or flu vaccines (e.g., FLU3 OR FLUR4), or COVID-19 and flu on the same date were excluded.

The MedDRA terms coded by VAERS were further aggregated by a clinician into clinically meaningful broader terms. For example, the terms "fever," "chills," "pyrexia," and similar terms were combined under the term "fever." The reported AEs in the results section used these broader terms. Mapping of MedDRA terms to broader categories is included in the Supplementary table (Supplemental Table-S1). All preprocessing of the data was informed by the VAERS Data Use Guide [12].

Statistical Analysis

Demographic characteristics were described for persons who reported AEs related to COVID-19 and flu vaccine use. After stratifying the data by age group, we tabulated the refined AEs and reported the 10 most frequently reported AEs for each age group and vaccine type. Risk ratios [13,14], also called relative risks, and associated 95 % confidence intervals (CI) were calculated for the top 10 AE for each age group and vaccine type. Relative risks (RR) were calculated using the formula:

$$RR = \frac{incidence\ in\ exposed\ (COVID-19\ vaccines)}{incidence\ in\ nonexposed\ (Flu\ vaccines)}$$

95% Confidence interval of RR were calculated, taking the antilog(exp) of the formula:

$$ln_{ln}(\widehat{RR}) \pm z\sqrt{\frac{(exposed\ without\ outcome)exposed\ with\ outcome}{Total\ exposed} + \frac{(nonexposed\ without\ outcome)nonexposed\ with\ outcome}{Total\ nonexposed}}$$

Data preprocessing and descriptive analyses were conducted using R version 4.0.2, running in RStudio Version 1.2.5033.

Results

Moderna had the highest number of AE reports (121,581), followed by Pfizer (100,752), Janssen (26,911) and Unknown COVID vaccine (456). For the same study period, there were 4,554 reports associated with all flu vaccines. Female patients reported more across all five study cohorts: Pfizer (70.6%), Moderna (75.5%), Janssen (63.3%), Unknown COVID vaccine (67.5%), and flu vaccines (72.0%). In addition, 31- to 64-year-olds provided the most reports across the five study cohorts: Pfizer (59.2%), Moderna (56.1%), Janssen (64.5%), Unknown COVID vaccine (62.5%), and flu vaccines (41.7%). More than 56% of Pfizer, Janssen, Unknown COVID vaccine, and flu vaccine reports had missing information on the type of medical attention received (Table 1).

Across the five cohorts, over a third of reports indicated recovery from the associated adverse effects. However, another third of reports indicated that they had not recovered from the vaccine-related adverse effects, which may be a result of the reporting system's use as an "event reporting" tool without a mechanism for follow-up reporting. The proportion of reported deaths was at a similar level across all COVID-19 vaccines, while the flu cohort had a reported death rate of 0.3% (Table 1). Most reports originated from the state of California for all five cohorts (Supplemental Table-S2).

Common AEs for COVID-19 and Flu Vaccines

For the 12 to 15-year age group, the most common AEs across the cohorts assessed were central neuropathy (e.g., dizziness, lightheadedness), fever, headache, chest pain, and hypotension (Supplemental Table-S3). In this same age group, persons receiving the first dose of Pfizer vaccine were 0.64 times less likely to experience pallor (95% CI: 0.44 to 0.95), 0.55 times less likely to experience hypotension (95% CI:0.45 to 0.68), and 0.49 times less likely to experience visual changes (95% CI: 0.32 to 0.73) than a person receiving flu vaccine. Persons receiving the second dose of Pfizer vaccine were 0.37 times less likely to experience central neuropathy than those receiving the flu vaccine (95% CI: 0.22 to 0.63) (Figure 2).

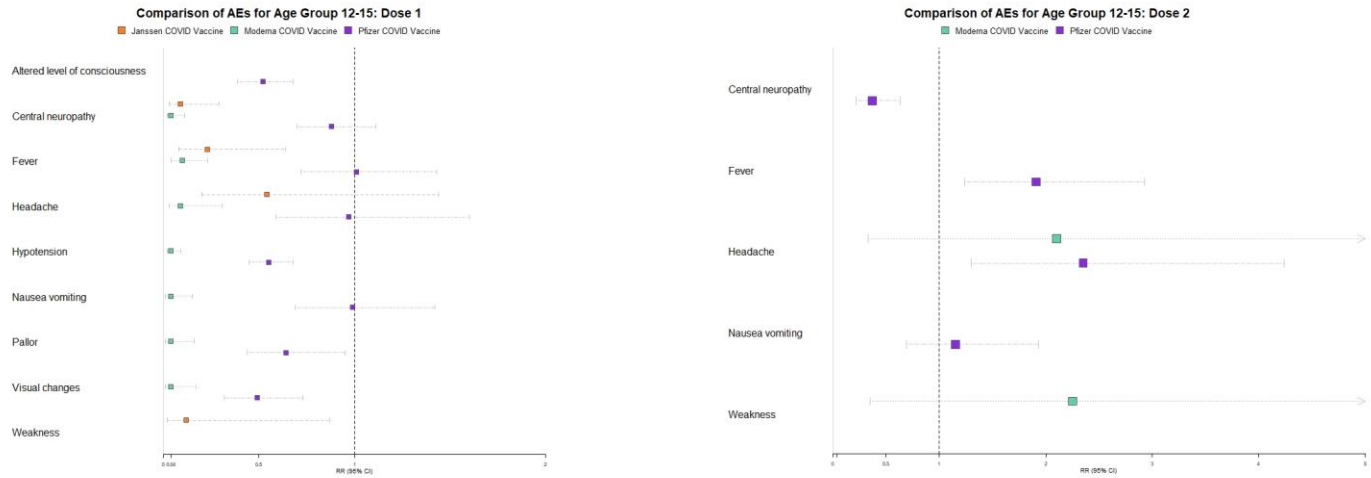
Persons from the 12 to 15-year age group who received the first dose of the Moderna vaccine were 0.1 times less likely to experience fever (95% CI: 0.04 to 0.23), 0.09 times less likely to experience headache (95% CI: 0.03 to 0.31), 0.04 times less likely to experience central neuropathy (95% CI: 0.02 to 0.11), 0.04 times less likely to experience hypotension (95% CI: 0.02 to 0.09), 0.04 times less likely to experience nausea/vomiting (95% CI: 0.01 to 0.15), 0.04 times less likely to experience pallor (95% CI: 0.01 to 0.16), and 0.04 times less likely to experience visual changes (95% CI: 0.01 to 0.17) than a person receiving the flu vaccine. RRs reported for persons receiving the second dose of Moderna vaccine were not statistically significant (Figure 2).

Persons receiving the first dose of the Janssen vaccine were 0.23 times less likely to experience fever (95% CI: 0.08 to 0.64), 0.12 times less likely to experience weakness (95% CI: 0.02 to 0.87), and 0.09 times less likely to experience central neuropathy (95% CI: 0.03 to 0.29) than persons receiving the flu vaccine (Figure 2).

Table 1: Characteristics of persons who reported use of Flu or COVID Vaccines during 2020 and 2021.

Characteristics	Pfizer Vaccine	Moderna Vaccine	Janssen Vaccine	Unknown COVID Vaccine	Combined Flu Vaccines
			Counts (%)		
	100,752	121,581	26,911	456	4,554
Sex (%)					
Female	71,142 (70.6)	91,810 (75.5)	17,024 (63.3)	308 (67.5)	3,281 (72.0)
Male	28,927 (28.7)	29,229 (24.0)	9,801 (36.4)	144 (31.6)	1,250 (27.4)
Unknown	683 (0.7)	542 (0.4)	86 (0.3)	4 (0.9)	23 (0.5)
Age Group (%)					
12-15	4,294 (4.2)	415 (0.3)	117 (0.4)	1 (0.2)	189 (4.2)
16-30	17,875 (17.7)	18,910 (15.6)	6,761 (25.1)	87 (19.1)	607 (13.3)
31-64	59,688 (59.2)	68,185 (56.1)	17,364 (64.5)	285 (62.5)	1,897 (41.7)
65+	18,895 (18.8)	34,071 (28.0)	2,669 (9.9)	83 (18.2)	1,861 (40.9)
Medical Attention Type (%)					
Emergency Visit	14,569 (14.5)	11,304 (9.3)	3,517 (13.1)	72 (15.8)	474 (10.4)
Hospitalized	5,930 (5.9)	5,259 (4.3)	1,679 (6.2)	43 (9.2)	121 (2.7)
Office Visit	17,016 (16.9)	19,288 (15.9)	4,350 (16.2)	76 (16.6)	1,394 (30.6)
Missing	63,237 (62.8)	85,730 (70.5)	17,365 (64.5)	265 (58.1)	2,565 (56.3)
Recovered (%)					
Yes	38,055 (37.8)	44,956 (37.0)	10,912 (45.5)	172 (37.7)	1,548 (34.0)
No	36,501 (36.2)	44,185 (36.3)	9,876 (36.7)	185 (40.6)	1,603 (35.2)
Unknown	16,418 (16.3)	23,468 (19.3)	4,322 (16.1)	69 (15.1)	1,067 (23.4)
Missing	9,778 (9.7)	8,972 (7.4)	1,801 (6.7)	30 (6.6)	336 (7.4)
Deaths (%)	1,343 (1.3)	1,491 (1.2)	313 (1.2)	8 (1.8)	15 (0.3)

Figure 2: Comparison of AEs for Age Group 12-15



For the 16 to 30-year age group, the most common AEs across the five-vaccine cohort were fever, central neuropathy, and injection site complications (Supplemental Table-S3). Persons receiving the first dose

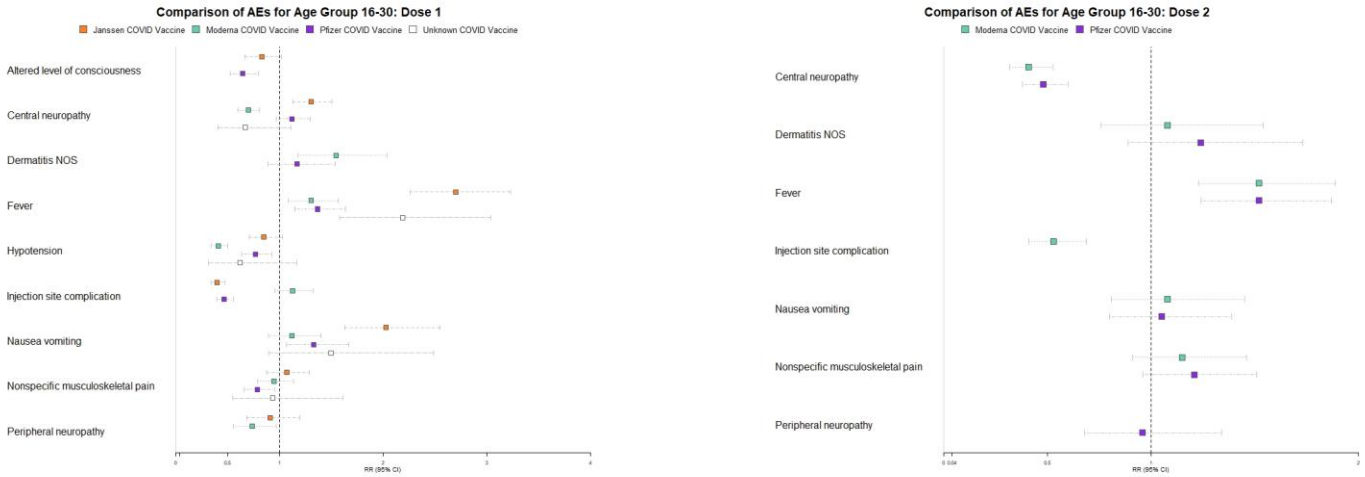
of the Pfizer vaccine were 1.37 times more likely to experience fever (95% CI:1.15 to 1.64), 0.79 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.66 to 0.96), 0.77 times less likely to experience hypotension (95% CI: 0.64 to 0.93), 0.65 times less likely to experience altered level of consciousness (95% CI: 0.53 to 0.8), and 0.47 times less likely to experience injection site complications (95% CI: 0.4 to 0.56) than a person receiving the flu vaccine. Persons receiving the second dose of the Pfizer vaccine were 1.52 times more likely to experience fever (95% CI:1.24 to 1.87) and 0.48 times less likely to experience central neuropathy (95% CI: 0.38 to 0.6) than a person receiving the flu vaccine (Figure 3).

Persons in the 16 to 30-year age group receiving the first dose of the Moderna vaccine were 0.74 times less likely to experience peripheral neuropathy (95% CI: 0.56 to 0.97), 0.7 times less likely to experience central neuropathy (95% CI: 0.6 to 0.81), and 0.4 times less likely to experience hypotension (95% CI: 0.34 to 0.5) than a person receiving flu vaccine.

Persons receiving the second dose of the Moderna vaccine were 1.52 times more likely to experience fever (95% CI: 1.23 to 1.89), 0.53 times less likely to experience injection site complications (95% CI: 0.41 to 0.69), and 0.41 times less likely to experience central neuropathy (95% CI: 0.32 to 0.53) than a person receiving the flu vaccine (Figure 3).

Persons receiving the Janssen vaccine were 2.03 times more likely to experience nausea/vomiting (95% CI: 1.63 to 2.55), 1.31 times more likely to experience central neuropathy (95% CI: 1.13 to 1.51), and 0.4 times less likely to experience injection site complications (95% CI: 0.34 to 0.48) than a person receiving the flu vaccine. Persons receiving the Unknown COVID vaccine were 2.19 times more likely to experience fever (95% CI: 1.58 to 3.04) compared to persons receiving the flu vaccine (Figure 3).

Figure 3: Comparison of AEs for Age Group 16-30



For the 31 to 64-year age group, the most common AEs across the five-vaccine cohort were fever, injection site complication, and headache (Supplemental Table-S3). Persons receiving the first dose of the Pfizer vaccine were 2.1 times more likely to experience headache (95% CI: 1.82 to 2.42), 1.91 times more likely to experience central neuropathy (95% CI: 1.67 to 2.2), 1.52 times more likely to experience nausea/vomiting (95% CI: 1.3 to 1.76), 1.2 times more likely to experience fever (95% CI: 1.09 to 1.32), 1.19 times more likely to experience peripheral neuropathy (95% CI: 1.04 to 1.36), 0.62 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.58 to 0.67), and 0.35 times less likely to experience injection site complications (95% CI: 0.33 to 0.37) than those receiving the flu vaccine (Figure 4).

Persons receiving the second dose of the Pfizer vaccine were 2.08 times more likely to experience headache (95% CI: 1.78 to 2.42), 1.27 times more likely to experience central neuropathy (95% CI: 1.09 to 1.49), 1.25 times more likely to experience nausea vomiting (95% CI: 1.05 to 1.48), 1.15 times more likely to experience fever (95% CI: 1.03 to 1.29), 0.76 times less likely to experience dermatitis NOS (95% CI: 0.65 to 0.89), 0.68 times less likely to experience nonspecific musculoskeletal pain

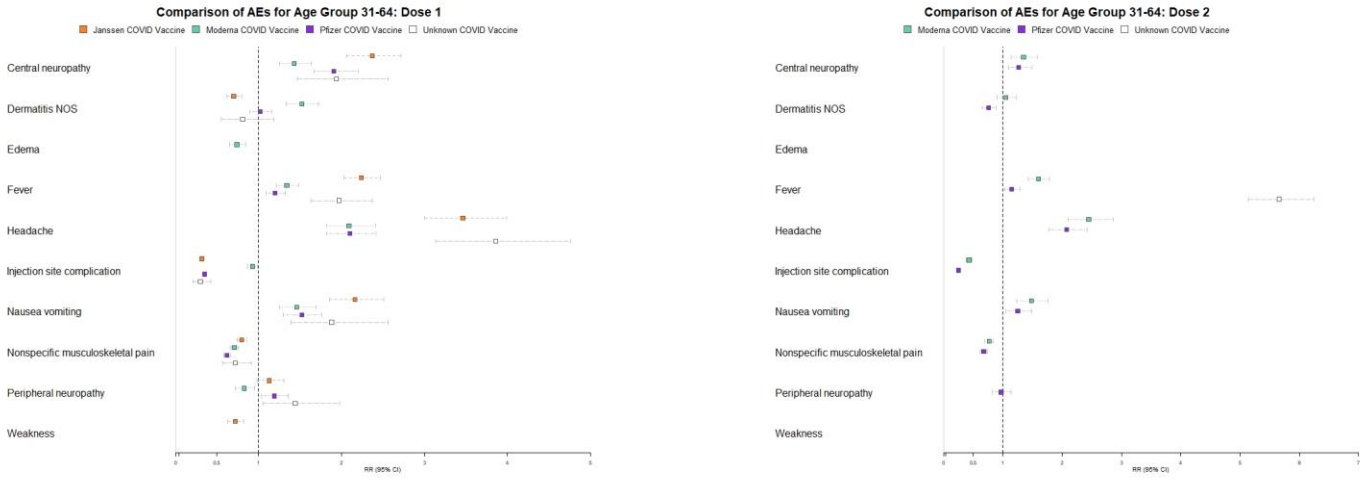
(95% CI: 0.62 to 0.74), and 0.25 times less likely to experience injection site complications (95% CI: 0.22 to 0.28) than a person receiving the flu vaccine (Figure 4).

Persons receiving the first dose of the Moderna vaccine were 2.09 times more likely to experience headache (95% CI: 1.82 to 2.41), 1.52 times more likely to experience dermatitis NOS (95% CI: 1.34 to 1.72), 1.46 times more likely to experience nausea/vomiting (95% CI: 1.25 to 1.69), 1.43 times more likely to experience central neuropathy (95% CI: 1.25 to 1.64), 1.34 times more likely to experience fever (95% CI: 1.21 to 1.48), 0.93 times less likely to experience injection site complications (95% CI: 0.87 to 0.99), 0.83 times less likely to experience peripheral neuropathy (95% CI: 0.72 to 0.95), 0.74 times less likely to experience edema (95% CI: 0.65 to 0.84), and 0.71 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.66 to 0.76) than a person receiving the flu vaccine (Figure 4). Persons receiving the second dose of the Moderna vaccine were 2.45 times more likely to get a headache (95% CI: 2.1 to 2.86), 1.6 times more likely to experience fever (95% CI: 1.43 to 1.79), 1.48 times more likely to get nausea vomiting (95% CI: 1.24 to 1.76), 1.35 times more likely to get central neuropathy (95% CI: 1.14 to 1.58), 0.77 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.7 to 0.84), and 0.43 times less likely to experience injection site complications (95% CI: 0.38 to 0.48) than a person receiving the flu vaccine (Figure 4).

Persons receiving the first dose of the Janssen vaccine were 3.46 times more likely to get a headache (95% CI: 3 to 3.99), 2.37 times more likely to get central neuropathy (95% CI: 2.06 to 2.76), 2.24 times more likely to get a fever (95% CI: 2.03 to 2.47), 2.16 times more likely to get nausea/vomiting (95% CI: 1.85 to 2.51), 0.8 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.74 to 0.86), 0.72 times less likely to experience weakness (95% CI: 0.63 to 0.82), 0.7 times less likely to experience dermatitis NOS (95% CI: 0.62 to 0.8), and 0.32 times less likely to experience injection site complications (95% CI: 0.29 to 0.34) than a person receiving the flu vaccine (Figure 4).

Persons receiving the first dose of the Unknown COVID vaccine were 3.86 times more likely to experience headache (95% CI: 3.13 to 4.76), 1.97 times more likely to experience fever (95% CI: 1.63 to 2.37), 1.94 times more likely to experience central neuropathy (95% CI: 1.47 to 2.56), 1.88 times more likely to experience nausea/vomiting (95% CI: 1.39 to 2.56), 1.44 times more likely to experience peripheral neuropathy (95% CI: 1.05 to 1.98), 0.72 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.57 to 0.91), and 0.3 times less likely to experience injection site complications (95% CI: 0.21 to 0.43) than a person receiving the flu vaccine (Figure 4).

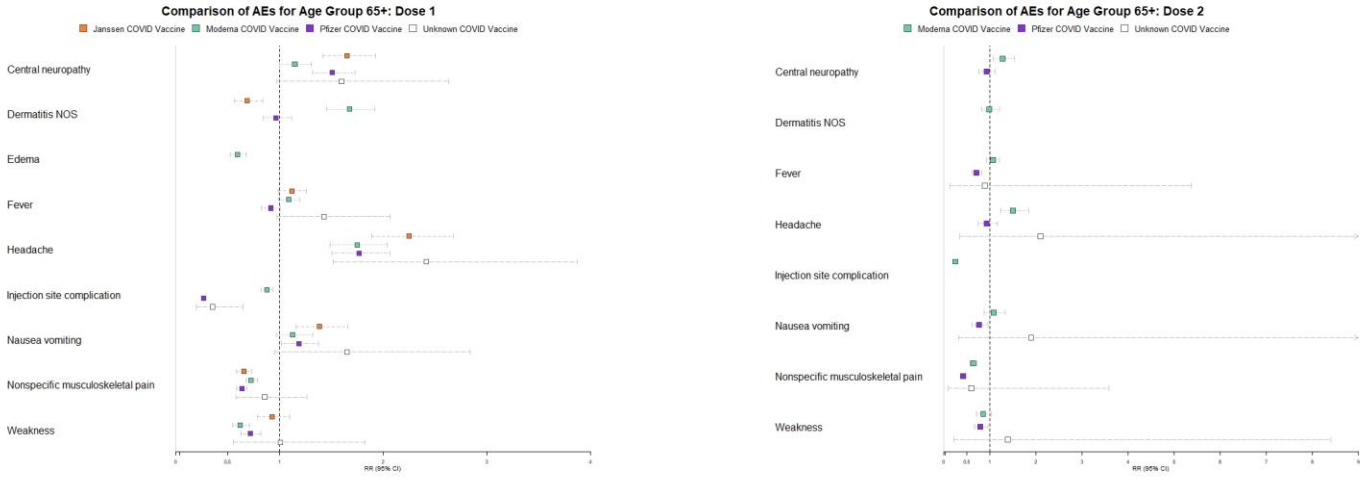
Figure 4: Comparison of AEs for Age Group 31-64



For the 65+ age group, the most common AEs across the five-vaccine cohort were fever, injection site complication, nonspecific musculoskeletal pain, and fatigue (Supplemental Table-S3). For 65+ age group, persons receiving the first dose of the Pfizer vaccine were 1.77 times more likely to experience headache (95% CI: 1.51 to 2.07), 1.51 times more likely to experience central neuropathy (95% CI: 1.3 to 1.73), 1.19 times more likely to experience nausea/vomiting (95% CI: 1.02 to 1.38), 0.72 times less likely to experience weakness (95% CI:

0.63 to 0.82), 0.64 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.59 to 0.69), and 0.27 times less likely to experience injection site complication (95% CI: 0.25 to 0.29) than a person receiving the flu vaccine. Persons receiving the second dose of Pfizer vaccine were 0.8 times less likely to experience weakness (95% CI: 0.67 to 0.96), 0.77 times less likely to experience nausea/vomiting (95% CI: 0.62 to 0.96), 0.71 times less likely to experience fever (95% CI: 0.62 to 0.82), and 0.42 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.37 to 0.49) than a person receiving the flu vaccine (Figure 5).

Figure 5: Comparison of AEs for Age Group 65+



Persons receiving the first dose of the Moderna vaccine were 1.75 times more likely to experience headache (95% CI: 1.49 to 2.04), 1.68 times more likely to experience dermatitis NOS (95% CI: 1.46 to 1.92), 0.88 times less likely to experience injection site complications (95% CI: 0.82 to 0.94), 0.73 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.68 to 0.79), 0.62 times less likely to experience weakness (95% CI: 0.55 to 0.71), and 0.6 times less likely to experience edema (95% CI: 0.53 to 0.68) than a person receiving the flu vaccine (Figure 5).

Persons receiving the second dose of the Moderna vaccine were 1.51 times more likely to experience headache (95% CI: 1.24 to 1.85), 1.28 times more likely to experience central neuropathy (95% CI: 1.07 to 1.53), 0.64 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.57 to 0.73), and 0.26 times less likely to experience injection site complications (95% CI: 0.22 to 0.31) than a person receiving the flu vaccine (Figure 5).

Persons receiving Janssen vaccine were 2.25 times more likely to experience headache (95% CI: 1.89 to 2.68), 1.65 times more likely to experience central neuropathy (95% CI: 1.42 to 1.93), 1.39 times more likely to experience nausea vomiting (95% CI: 1.16 to 1.66), 0.69 times less likely to experience dermatitis NOS (95% CI: 0.57 to 0.84), and 0.66 times less likely to experience nonspecific musculoskeletal pain (95% CI: 0.59 to 0.73) than a person receiving the flu vaccine (Figure 5).

Persons receiving the Unknown COVID vaccine were 2.42 times more likely to experience headache (95% CI: 1.52 to 3.87) and 0.36 times less likely to experience injection site complications (95% CI: 0.2 to 0.65) than a person receiving flu vaccine (Figure 5).

Apart from the frequently reported AEs (Figure 2-5), some AEs were worth mentioning due to the growing concerns in the media, such as Guillain Barre Syndrome [15] and gynecologic changes [16]. Since these concerns were specific to the COVID-19 vaccine and rarely reported as AEs for the flu vaccines, RR statistics were not calculated.

Discussion

As mentioned previously, the interpretation of these results is subject to the limitations of a passive surveillance system. The COVID vaccines are all new, and reporting of AEs is likely far more robust than that of the influenza vaccines, where adverse events associated with flu vaccines are well understood and more likely to go unreported. As a result, the raw counts make the COVID vaccines appear to be associated with substantially more AEs than influenza vaccines. The relatively low utilization

of flu vaccines (43.0% of the U.S. population during the 2010-2011 season)[17] may further compound this discrepancy and make true comparisons difficult as power calculations were not performed.

Moderna had the highest number of reports in the VAERS database across all age groups. Most of the reports were from the 31- to 64-year age group, which likely could be a result of the vaccines being authorized for this age group first. The proportion of reports was equally divided among those having recovered and not recovered from the AEs across all cohorts. Across the five cohorts and age groups, common AEs could be summarized as central neuropathy (e.g., dizziness, lightheadedness), fever, headache, injection site symptoms, nonspecific musculoskeletal pain, and chest pain. Except for chest pain, most of the AEs were already identified in randomized controlled clinical trials of COVID-19 vaccines [5,6,18,19]. This is reassuring and further confirms the strength of our design and findings.

Investigating rare side effects of any vaccine is a difficult task [20] due to the rarity of those side-effects, the extended period of manifestation for some side-effects, and the lack of evidence for causation from observational studies. However, observational studies such as this are often a good starting point to inform randomized trials [21]. A list of all side effects, including rare side effects, have been reported in Supplemental Table-S3. A robust surveillance system (i.e a combination of active and passive surveillance systems) is key in documenting rare AEs and generating hypotheses for future randomized controlled trials.

The two main strengths of this study are providing a list of all AEs, including the rare ones, and using RRs combined with 95% confidence intervals to assess the strength of association between common AEs of flu and COVID-19 vaccines. However, this study was limited to only those populations who reported having AEs on any COVID-19 or Flu vaccine. Therefore, this can limit the generalizability of our findings due to potential differences in the general population from the study population. It is also important to note that some AEs occurred more with flu vaccines than with COVID-19 vaccines. For example, for the 12- to 15-year age group, seizures were reported with 7% of the flu vaccines given but only 3-4% for COVID-19 vaccines. Similarly, for the 65+ age group, edema was reported for 12% of the flu vaccines given but only 2-7% for COVID-19 vaccines. These common AEs for both vaccines can serve as evidence for randomized trials; furthermore, comparison of AE profiles can also inform the public regarding their decision to receive a vaccine (i.e., to aid in overcoming a component of vaccine hesitancy).

An additional limitation of this study is the lack of severity data for the various AEs. For example, fever and headache are not generally considered a concerning symptom; however, severe fever and headache may disrupt a person's daily life, such as, if they require time off from work due to the subsequent pain and discomfort. There are some inherent limitations of the VAERS database as well. Multiple AE reports in the VAERS database indicate a potential association between vaccine and AEs, but these associations should not be implied as causal [12]. As with any passive surveillance system, VAERS is susceptible to underreporting and incomplete data [12]. Finally, regarding the determination of causality, some changes could be made to the VAERS data collection that might allow better understanding of the quality of the data. Based on our experience, we would suggest VAERS collect data while also indicating the origin of the AE report (e.g., Individual or Institutions (i.e., include public identifiers like CMS Certification Number (CCN), National Provider Identifier (NPI)). Including the source of the VAERS report in the database would help researchers filter the data by report origin type, thus facilitating more robust study designs and reporting based on the potential quality of the data. This, in turn, may lead to a better resolution when determining causality.

Conclusion

Based on the available data and our results, the short-term AE profiles between flu and COVID-19 vaccines were very similar. Continued vaccine safety monitoring and ongoing advocacy targeting the public to report AEs associated with COVID-19 vaccines to the VAERS will help researchers identify AEs causally related to vaccines and generate hypotheses for further investigations. Although a relatively newer technology, mRNA vaccines appear to have a similar safety profile to the long-used yearly influenza vaccines. The current study can be used to inform decision-making about COVID-19 and flu vaccinations and potentially overcome an aspect of vaccine hesitancy.

Competing Interests

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

Ethics Approvals

Since our study used de-identified data from a publicly available health surveillance system, IRB review was not required.

Contributions

PMP and CL conceived of study design, performed data analysis and finalized the manuscript in collaboration with ZS and MJR. MJR classified the MedDRA terms into clinically meaningful categories and provided input on implications of the findings. All authors contributed equally towards the preparation of this manuscript.

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