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Original article

Comparison of the post-marketing safety profile between influenza and COVID-19 vaccines: An analysis of the vaccine adverse event reporting system

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ABSTRACT

The global coronavirus disease (COVID-19) epidemic can be partially managed by vaccines; however, the public must be informed about the safety of COVID-19 vaccines to avoid hesitancy. Therefore, it is important to know the safety profile of the COVID-19 vaccine by comparison to that of a well-known vaccine, such as the influenza vaccine. Hence, this retrospective descriptive study was conducted to evaluate and compare the number of adverse effects (AEs) reported to the Vaccine Adverse Event Reporting System (VAERS) for both COVID-19 and influenza vaccines, identify the most common AEs of each vaccine, and compare the frequency and outcomes of using COVID-19 and influenza vaccines in the U.S. population. Surveillance reports from 1st December 2020 to 8th October 2021 of both vaccines were retrieved from the U.S. VAERS. A total of 544,025 and 15,871 reports of post-COVID-19 and - influenza vaccine AEs were reported to the VAERS, respectively. Females reported > 58% and nearly 70% of influenza - and COVID-19 vaccine-associated AEs, respectively. The estimated incidence rates of AEs associated with COVID-19 and influenza vaccines in the U.S. were 1.36 and 0.12 per 1,000 persons, respectively. The incidence of AEs was higher among COVID-19 vaccine recipients than that among influenza vaccine recipients. COVID-19 vaccine recipients have a two-fold higher risk of mortality and life-threatening events than influenza vaccine recipients. However, most of the reported AEs were similar between the two vaccines in terms of symptoms.

1. Introduction

Coronavirus disease (COVID-19) is caused by a new coronavirus that was discovered in December 2019 in Wuhan (Lu et al., 2020), and in March 2020, the World Health Organisation (WHO) declared COVID-19 a pandemic (WHO, 2020). The COVID-19 pandemic has had an undesirable effect on global healthcare systems and life (Nicola et al., 2020). The severity of COVID-19 symptoms varies, and disease severity ranges from asymptomatic/mild to severe illness and death (Esakandari et al., 2020).

COVID-19 primarily affects the respiratory system, but other organ systems can also be affected (Yuki et al., 2020). Lower respiratory tract infection-related symptoms include dry cough, dyspnoea, and fever (Huang et al., 2020). In addition, dizziness, headache, diarrhea, generalized weakness, and vomiting have also been reported (Shi et al., 2020). Of note, anyone can contract COVID-19 and become seriously ill or die at any age, but some individuals, such as persons aged 60 years or more; pregnant women; or those with underlying medical problems, such as heart and lung problems, high blood pressure, obesity, cancer, and diabetes, are at an increased risk of developing COVID-19 (WHO, 2021a).

COVID-19 vaccination helps protect children and adults and their close contacts from getting sick or severely ill with COVID-19 (CDC, 2021a). Vaccination against COVID-19 reduces hospitalization risk, prevents infection outbreaks, and reduces mortality rates (CDC, 2021c). Currently, three COVID-19 vaccines have been approved by the Food and Drug Administration (FDA) for use in the

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United States as follows: Pfizer-BioNTech, Moderna, and Janssen (AAFP, 2021). Both Pfizer-BioNTech vaccine and Moderna vaccine are considered mRNA vaccines while Janssen vaccine is an adenoviral vector vaccine (Edwards and Walter, 2022).

Vaccination against COVID-19 can substantially impact COVID-19 outbreaks, even with limited protection against infection (Moghadas et al., 2021); however, it may cause adverse effects (AEs). Maglione et al. (2014) stated that some vaccines are associated with serious AEs; nonetheless, these events are extremely rare and must be weighed against the numerous benefits that vaccines provide. Kaur et al. (2021) reported that commonly reported local COVID-19 vaccine-associated AEs include injection site pain, redness, and swelling. Systemic reactions include fatigue, fever, headache, and myalgia. Furthermore, Kaur et al. (2021) reported that COVID-19 vaccines could be safe; however, long-term post-marketing surveillance data, especially in the elderly and those with comorbidities, children, and pregnant women, are warranted to ensure their safety.

Influenza vaccines have been in use for>60 years and have been safely administered to millions worldwide (WHO, 2022a). Influenza vaccines are generally safe but can cause common side effects, such as headaches, soreness, redness, swelling, nausea, fever, and muscle aches (CDC, 2019). In the United States, there are several influenza vaccine manufacturers and a variety of influenza vaccination products that are licensed and recommended for usage. Quadrivalent inactivated influenza vaccine (IIV4), recombinant influenza vaccine (RIV4), and live attenuated influenza vaccine (LAIV4) are all available influenza vaccines (CDC, 2021b).

The Vaccine Adverse Event Reporting System (VAERS) is an early warning system that monitors the safety of vaccines after they are authorized or licensed for use by the FDA. It accepts and analyses the reports of possible AEs after vaccination (CDC, 2021d). If a vaccine is suspected to cause AEs, the FDA will further investigate and take the required action if needed (CDC, 2021d).

Vaccines for influenza have been used for almost 75 years and are largely trusted and regarded as safe. In such circumstances, it is normal for the public and professionals to compare the safety profiles of COVID-19 and influenza vaccinations, including adverse events. These comparisons will be helpful in filling up the evidence gap in communicating the safety risks associated with COVID-19 vaccination and so overcoming one of the factors that contribute to vaccine apprehension. It is important to know the safety profile of the COVID-19 vaccine and to compare it with that of a well-known vaccine, such as the influenza vaccine. Thus, our study was conducted to evaluate the reports submitted to the VAERS pertaining to the influenza vaccine and the COVID19 vaccine, compare the number of AEs associated with COVID-19 and influenza vaccines, and identify the most common AEs of each vaccine.

2. Materials and methods

2.1. Study design

This study was a retrospective descriptive and comparative database analysis of AE reports after COVID-19 and influenza vaccines from 1st December 2020 to 8th October 2021 using submitted reports to the U.S. VAERS.

2.2. Study population

Reports on either COVID-19 or influenza vaccines were retrieved. To mimic the FDA approval recommendations that restrict the use of COVID-19 and influenza vaccines for some age groups (≥12 years vs. > 6 months, respectively) (FDA, 2022a; FDA, 2022b), we obtained COVID-19-related reports for individuals aged ≥ 12 years. In contrast, we extracted influenza vaccine-related reports for individuals older than six months of age. Duplicate and incomplete reports were excluded from this study. Furthermore, reports of persons who simultaneously received both vaccines were excluded to minimize bias and improve the integrity of our comparison.

2.3. Data source

We retrieved all reports for either COVID-19 or influenza vaccines using the U.S. VAERS to monitor safety. The Vaccine Adverse Event Reporting System (VAERS) is a passive reporting system, which means it relies on people to send in reports about their negative reactions to vaccines. The VAERS is available to the public; however, all patient and reporter identifiers have been removed and made anonymized. It was established in 1990 to facilitate the early detection of vaccine-related safety issues in the United States. Although it is supervised by the CDC and the FDA, manufacturers, physicians, pharmacists, nurses, patients, and patients' relatives can submit reports concerning vaccine-related adverse effects. The database, which includes data from as far back as 1990, takes no more than six weeks to process newly submitted reports. Generally, the data is composed of three main files (VAERS data file, VAERS vaccine file, and VAERS symptom file). The VAERS data file provides information about the patient (age, gender, and allergies), the consequences (death, hospitalization, life-threatening, ER visit, office visit, disability, and birth defects), and the report (vaccine date, report date, adverse effect onset data, days to onset, recover date, and prior vaccinations). The VAERS vaccine file contains information about the vaccine such as type, route of administration, dose series, vaccine name, and manufacture. Finally, the VAERS symptom file is composed of the recorded symptoms for each report. All files have a unique VAERS identification number that allows merging, extracting, and analysing the data.

2.4. Data Variables

The study included patient-related data, such as sex, age, vaccine series, days to event onset, and the institution where the vaccine was administered. Moreover, it included AE-related data (symptoms).

2.5. Statistical data analysis

Descriptive statistical analyses were used to summarise the baseline characteristics of our study population using mean ± standard deviation and/or median for continuous variables. In addition, frequency and percentages were used for categorical variables. Comparisons of variables between patients who received COVID-19 vaccines vs. influenzas vaccines were performed using Student's t-tests if they are continuous, and Chi-square tests if they were categorical. We applied the incidence equation (1) to calculate the estimated incidence of AEs for each vaccine type as follows:

$$\text{Estimated incidence} = \frac{\text{total number of new AEs}}{\text{total number of administered vaccine doses for the same period}} \times 1000 \quad (1)$$

The total number of administered doses for both COVID-19 and influenza vaccines was retrieved from the Centers for Disease Control and Prevention (CDC) vaccine tracker website up to October 8,

2021. A two-tailed p-value < 0.05 was considered statistically significant. All analyses were performed using SAS software and MS Excel.

3. Results

Between 1st December 2020 to 8th October 2021, the VAERS received 544,025 and 15,871 reports for COVID-19 and influenza vaccines, respectively. The estimated incidence of AEs for both vaccines is presented in Table 1.

Table 2 shows the baseline characteristics of the study participants. The age-group comparisons between the two vaccine groups were significantly different (p <.0001). Most Pfizer® (72.27%) and Moderna® (79.88 %) vaccine recipients were older than 35 years. The majority (85.64%) of Janssen vaccine recipients were between 18 and 64 years of age, and approximately two-thirds of the influenza vaccine users were older than 35 years of age (66.72%).

In addition, the gender-group comparisons between the two vaccine groups were significantly different (p <.0001). Interestingly, females reported more AEs than males, regardless of the vaccine type, which accounted for > 68% of influenza vaccine-associated AEs. Females also accounted for most of the population with COVID-19 vaccine-associated AEs.

Influenza vaccines were administered mainly at pharmacies (56%). In contrast, only 23.66%, 25.44%, and 33.32% of the Pfizer, Moderna, and Janssen vaccines were administered at pharmacies.

Table 3 shows the dose series of the vaccines and the onset of AEs. Some patients who received COVID-19 and influenza vaccines reported AEs after the first dose; >93%, 57%, 66.89%, and 98.82% of patients had AEs after the first dose of influenza, Pfizer, Moderna, and Janssen vaccines, respectively.

>59%, 46.65%, 40.19%, and 49.86% of the patients who received influenza, Pfizer, Moderna, and Janssen vaccines, respectively, reported that the AEs occurred within the same day of vaccine administration.

Table 4 shows the consequences of the reported AEs of different vaccines. Between 1.23 and 1.33% of COVID-19 vaccine reports were associated with patient mortality, which is two-fold the deaths associated with influenza vaccine reports (0.66%). Similarly, life-threatening events were reported more frequently among COVID-19 vaccine recipients than among influenza vaccine recipients; 1.81%, 1.34%, 2.4%, and 0.79% life-threatening events were reported for Pfizer, Moderna, Janssen, and influenza vaccines, respectively.

The percentage of reported disabilities was similar (nearly 1.7%) for both vaccine types. Furthermore, although the rate of birth defects was low among recipients of both vaccine groups (Pfizer [0.07%], Moderna [0.05%], Janssen [0.06%], and influenza vaccines [0.08%]), it is difficult to know the total number and percentage of pregnant women among the female reporters as the available data didn't include if the female was pregnant or not during the occurrence of the adverse events because pregnancy is not one of the variables that are written in the reports.

Emergency room (ER) and physician office visits were the most reported consequences of both vaccines. Approximately 23.29% and 20.6% of influenza and COVID-19 vaccine recipients reported visiting the physician's office, respectively. In contrast, COVID-19 vaccine recipients reported more ER visits (13.85%) than the influenza vaccine recipients (9.37%).

Hospitalization due to AEs was higher among Janssen and Pfizer vaccine recipients (>7%), followed by Moderna (5.15%) and influenza vaccine (3.29%) recipients. Nevertheless, influenza vaccine recipients generally stayed one day longer than COVID-19 vaccine recipients.

Table 5 shows the ten most reported AEs of each vaccine. The most reported AEs among Pfizer and Moderna vaccine recipients were headaches (18.95% vs 19.61%), fatigue (15.93% vs 16.74%), and pyrexia (14.40% vs 17.78%). Similarly, the most reported AEs among those who received the Janssen vaccine were headache (31.94%), pyrexia (26.92%), and chills (23.25%). However, the most reported AEs among influenza vaccine recipients were a pain in the extremities (11.31%), general pain (10.62%), and injection site pain (9.27%).

Table 1
Estimated incidence for adverse effects reported for each vaccine type.

Vaccine type	Number of reports	Total number of doses*	Estimated incidence
Covid-19	544,025	401,453,944	1.355137
Influenza	15,871	132,500,000	0.119781

* The total number of administered doses for each vaccine was obtained from the CDC dose-tracking website until October 8, 2021.

4. Discussion

The safety of vaccines is critical for the successful implementation of all vaccination programmes, particularly during global outbreaks (Lee, 2021). Currently, in the absence of effective COVID-19 therapy to halt the spread of the coronavirus, the availability of effective and safe COVID-19 vaccines is important for the recovery of social and economic status from continuous disruption and ultimately, for the establishment of herd immunity (Tao et al., 2021). Previous studies have shown that some of the common reasons for COVID-19 vaccine hesitancy include safety concerns, particularly, regarding vaccine side effects (Callaghan et al., 2020; King et al., 2021; Lucia et al., 2020).

Our results show that the estimated incidence of AEs associated with COVID-19 vaccines in the U.S. was higher than that associated with influenza vaccines. Females reported more AEs than males, regardless of the vaccine type, and this is rational because females mount stronger innate and adaptive immune responses than males (Klein and Flanagan, 2016). Moreover, Beatty et al. (2021) reported that several factors, including sex and age, are associated with greater chances of showing AEs.

All COVID-19 vaccine recipients investigated in this study were ≥ 12 years because, in 2020, COVID-19 vaccines were not approved for children in the U.S. Notably, we found that most Pfizer and Moderna vaccine recipients were ≥ 35 years old. The majority of Janssen vaccine recipients were between 18 and 64 years old, and more than half of the influenza vaccine recipients were older than 35 years. The CDC reported that > 88% of individuals aged 18–55 years and > 79% of older individuals who received the Pfizer COVID-19 vaccine reported at least one local reaction (CDC, 2021e). Moreover, the CDC reported that the rate of local reactions to the Moderna COVID-19 vaccine was higher in persons aged 18–64 years than that in those aged ≥ 65 years (CDC, 2021f) and that the occurrence of any local reaction to the Janssen vaccine was higher in participants aged 18–59 years than that in those aged ≥ 60 years (CDC, 2021g).

Most of the patients who received influenza, Pfizer, Moderna, and Janssen vaccines reported that the AEs occurred within the same day or 2 days after receiving the vaccine. Most AEs were reported after the first dose of the vaccine had been administered, and most of the side effects occurred within the first three days of vaccination and disappeared within 1–2 days (Saudi Ministry of Health, 2022). WHO reported that side effects generally occur within the first few days of receiving the COVID-19 vaccine (WHO, 2021b). Moreover, Menni et al. (2021) found that local and systemic symptoms usually last 1–2 days after vaccine admin-

Table 2
The baseline characteristics of the study participants.

Variable	Pfizer vaccine N (%)	Moderna vaccine N (%)	Janssen vaccine N (%)	Influenza vaccine N (%)	Chi-Square
Age					
< 12	NA	NA	NA	2262 (14.25%)	< 0.0001
12–17	14,761 (6.17%)	5808 (2.25%)	1023 (2.24%)	952 (6.00%)	
18–34	51,581 (21.56%)	46,117 (17.86%)	12,923 (28.33%)	2067 (13.02%)	
35–49	64,216 (26.85%)	61,429 (23.79%)	12,757 (27.97%)	1952 (12.30%)	
50–64	60,427 (25.26%)	66,904 (25.91%)	13,383 (29.34%)	3370 (21.23%)	
≥65	48,213 (20.16%)	77,916 (30.18%)	5524 (12.11%)	5268 (33.19%)	
Gender					
Female	167,511 (70.03%)	189,063 (73.23%)	28,483 (62.45%)	10,808 (68.10%)	< 0.0001
Male	71,687 (29.97%)	69,111 (26.77%)	17,127 (37.55%)	5063 (31.90%)	
Vaccination location					
Private clinics	86,329 (36.09%)	76,140 (29.49%)	7964 (17.46%)	2671 (16.83%)	< 0.0001
Pharmacy	56,588 (23.66%)	65,667 (25.44%)	15,197 (33.32%)	8854 (55.79%)	
Other	96,281 (40.25%)	116,367 (45.07%)	22,449 (49.22%)	4346 (27.38%)	

N, total number.

Table 3
The dose series of the vaccines and the onset of developing adverse effects.

Variable	Pfizer vaccine N (%)	Moderna vaccine N (%)	Janssen vaccine N (%)	Influenza vaccine N (%)	Chi-Square
Vaccine dose series					
First	136,345 (57.00%)	172,692 (66.89%)	45,073 (98.82%)	14,764 (93.03%)	< 0.0001
Subsequent	102,853 (43.00%)	85,482 (33.11%)	537 (1.18%)	1107 (6.97%)	
Day to adverse effects onset					
Same day	111,583 (46.65%)	103,772 (40.19%)	22,741 (49.86%)	9443 (59.50%)	< 0.0001
After 1 or 2 days	64,316 (26.89%)	65,883 (25.52%)	9901 (21.71%)	4361 (27.48%)	
After ≥ 3 days	63,299 (26.46%)	88,519 (34.29%)	12,968 (28.43%)	2067 (13.02%)	

N, total number.

Table 4
Consequences for reported adverse effects classified by each vaccine type.

Reported Consequences	Pfizer vaccine (239,198)	Moderna vaccine (258,174)	Janssen vaccine (45,610)	Influenza vaccine (15,871)
Death	3,158 (1.32%)	3,168 (1.23%)	608 (1.33)	104 (0.66%)
Life-threatening event	4,334 (1.81%)	3,464 (1.34%)	1,096 (2.40%)	126 (0.79%)
Disability	4,447 (1.86%)	3,322 (1.29%)	899 (1.97%)	280 (1.76%)
Birth defects	171 (0.07%)	125 (0.05%)	27 (0.06%)	12 (0.08%)
Office visit	54,194 (22.66%)	47,690 (18.47%)	10,052 (22.04%)	3,696 (23.29%)
Emergency room visit	38,516 (16.10%)	27,793 (10.77%)	7,410 (16.25%)	1,487 (9.37%)
Hospitalisation	17,153 (7.17%)	13,300 (5.15%)	3,557 (7.80%)	522 (3.29%)
Median length of stay (days)	3	3	3	4

Table 5
The ten most reported adverse effects of each vaccine.

Symptoms	Pfizer vaccine (239,198)	Moderna vaccine (258,174)	Janssen vaccine (45,610)	Influenza vaccine (15,871)
Headache	18.95%	19.61%	31.94%	6.40%
Fatigue	15.93%	16.74%	21.73%	–
Pyrexia	14.40%	17.78%	26.92%	8.65%
Pain	13.27%	14.21%	21.73%	10.62%
Dizziness	12.89%	15.67%	16.91%	5.44%
Chills	12.55%	9.86%	23.25%	5.61%
Nausea	11.21%	11.11%	16.48%	–
Pain in extremity	9.39%	11.94%	12.58%	11.31%
Dyspnoea	6.73%	–	7.83%	–
Arthralgia or Myalgia	6.60%	–	8.52%	–
Injection site erythema	–	8.54%	–	7.13%
Injection site pain	–	8.51%	–	9.27%
Injection site swelling	–	–	–	6.33%
Erythema	–	–	–	6.38%

istration. FDA reported that the observed side effects of the Moderna vaccine typically lasted numerous days and most of the individuals who had received the vaccine experienced side effects after the second dose (FDA, 2022c).

According to our findings, between 1.23 and 1.33% of COVID-19 vaccines were associated with patient mortality. Moreover, the ratio of deaths and life-threatening events was two folds higher in the COVID-19 vaccine recipients than that in the influenza vaccine recipients. COVID-19 vaccine recipients also reported more ER visits than their influenza vaccine counterparts. Furthermore, hospitalization due to AEs was higher among COVID-19 vaccine recipients than that among influenza vaccine recipients. However, the

percentage of reported disabilities was similar (nearly 1.7%) for both types of vaccines. Nonetheless, influenza vaccine recipients usually stayed one day longer than COVID-19 vaccine recipients. The length of stay in the hospital was longer after receiving the influenza vaccine, which could be related to the fact that most of the influenza vaccine recipients were older patients. It is strongly recommended that people over the age of 65 get immunized against influenza every year because they are at a higher risk of serious complications from influenza than other healthy adults. The rate of birth defects was exceptionally low among recipients of both vaccines (0.05%–0.08%). The reported physician office visits due to the influenza vaccine (23.29%) were higher than those due to COVID-19 vaccines (20.6%). Of note, the European Medicines Agency stated that most of the known side effects of COVID-19 vaccines are short-lived, mild, and serious safety problems are rare (EMA, 2021). Furthermore, WHO has reported that serious and long-lasting side effects of COVID-19 vaccines are extremely rare (WHO, 2022b). McNeil et al. (2016) reported that anaphylaxis after COVID-19 mRNA vaccination was observed more frequently than the estimated rate after receiving influenza and other vaccines. Aimi et al. (2021) reported that the adverse reactions reported by participants who received the COVID-19 vaccine were mild to moderate and continued for a short duration. They also stated that no deaths were reported among COVID-19 vaccine recipients (Azimi et al., 2021).

The most reported AEs among COVID-19 vaccine recipients were headache, fatigue, pyrexia, pain, dizziness, chills, and nausea. The New Zealand Ministry of Health reported that the most reported reactions to the COVID-19 vaccine were pain or swelling at the injection site, headache, feeling tired or fatigued, muscle aches, joint pain, chills, nausea, redness at the injection site, and fever (New Zealand Ministry of Health, 2022). Furthermore, several randomized clinical trials of COVID-19 vaccines have reported that the AEs included systemic effects (such as headache, fatigue, and muscle or joint pain) and injection site events (such as redness, pain, and swelling), with rare serious AEs (Baden et al., 2021; Polack et al., 2020; Sadoff et al., 2021; Voysey et al., 2021).

The most reported AEs among the influenza vaccine recipients were pain, especially in the extremities, and injection site pain. Kim et al. (2022) reported that systematic reactions, such as fatigue, chills, and myalgia, were more noticeable with the mRNA COVID-19 vaccine. In contrast, injection site reactogenicity events are more common with influenza vaccines. The Office of Infectious Disease and HIV/AIDS Policy reported that side effects of the influenza vaccine might include headache, injection site side effects, muscle aches, upset stomach, and fever (HHS, 2021). Dikmen et al. (2019) reported that non-severe side effects, such as fever, local pain, headache, and muscle pain were observed in individuals who received influenza vaccination. Similarly, Torruella et al. (2013) reported that the most common AE of the influenza vaccine was a local reaction.

There are some limitations to this study that need to be considered. The first limitation of the study was that the information in VAERS reports may be inadequate, erroneous, coincidental, or unverifiable. VAERS reports can potentially be biased. As a result, there are restrictions on how the data can be used in science. The second limitation was that the number of reports alone cannot be construed as proof of a causative link between a vaccine and an adverse event, or as proof of the existence, severity, frequency, or incidence of vaccine-related problems.

Future research combining VAERS with other data sources will be crucial for vaccine surveillance, especially as newly marketed vaccines continue to be widely used in clinical practice. In addition, population-based longitudinal observational studies with propensity-score matching to minimize the baseline differences between COVID-19 and Influenza vaccine recipients are recommended.

5. Conclusions

Most reported AEs were similar for both COVID-19 and influenza vaccines. Nonetheless, the incidence of AEs after receiving the COVID-19 vaccine was higher than that after receiving the influenza vaccine. These AEs after immunization may or may not be associated with vaccination. Therefore, well-controlled studies are needed to test our findings and confirm the causal relationship between vaccine types and reported symptoms and consequences.

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.

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