Original article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Reactogenicity to COVID-19 vaccination in the United States of America

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Purpose: In the United States, Pfizer-BioNTech, Moderna, and Janssen's coronavirus disease 2019 (COVID-19) vaccines have been granted Emergency Use Authorization (EUA) with the Pfizer-BioNTech vaccine presently approved by the US Food and Drug Administration. The purpose of this study is to analyze passive surveillance data on COVID-19 vaccine adverse reaction in the United States.

Materials and Methods: We analyzed passive surveillance data on COVID-19 vaccine adverse reactions which were retrieved from the Vaccine Adverse Event Reporting System database. Retrieved records on demographic information as well as the top 10 common vaccine adverse events were extracted and assessed from 200 of the most recently reported cases for the study analysis.

Results: Local and systemic adverse reactions were reported in the study. A significant difference ($p<0.05$) was recorded for the top 10 systemic reactions by age category (0.041) and by gender (0.002). Analysis of the top five systemic reactions, stratified by vaccine type yielded a significant difference ($p<0.05$) for chills ($p=0.044$), and when stratified by age group and type of vaccination received, it yielded a significant difference ($p<0.05$) for fatigue ($p=0.023$). Overall, Pfizer had 182 persons (91.0%) reporting adverse events, Moderna with 13 (6.5%), and Janssen with 5 (2.5%).

Conclusion: Mild side effects were reported following vaccination with the EUA COVID-19 vaccines in the United States. Thus, continuous monitoring and reporting of all adverse events are recommended to ensure the safety of vaccination.

Keywords: COVID-19, SARS-CoV-2, Vaccination, Injection site reaction, Safety

Introduction

In December 2020, the world celebrated the Emergency Use Authorization (EUA) for the first coronavirus disease 19 (COVID-19) vaccine developed by Pfizer and Bio-N-Tech, an mRNA-based vaccine that yields 90% plus efficacy in preventing and limiting the deadly COVID-19 [1]. There was a glimpse of hope that the disease would soon be conquered, and life would return to normalcy. Soon afterward, the Moderna vaccine, also an mRNA-based vaccine, and the Janssen (Johnson and Johnson) vaccine, an adenovirus viral vector vaccine, gained EUA in the United States [1]. A new prerogative was set to vaccinate the whole world population. These vaccines (Pfizer and Moderna) were deemed to be part of the most efficacious vaccines ever known to humans using

a breakthrough technology of delivering protection through the mRNA [2]. Millions raced to get the vaccine as governments around the world struggled to keep up with the demand. As the vaccinated population grew, side effects and adverse events were reported with the use of these vaccines [3].

Besides the normal expected adverse events for vaccines such as injection site pain, fatigue, and fever; other systemic symptoms and reactions proved to be highly complicated and serious [4]. A small fraction of those receiving the Janssen vaccine suffered a rare cerebral venous sinus thrombosis (CVST) [5]. Serious side effects also occurred in those receiving the mRNA vaccines [4]. Between February and April 2021, there were several reports from recipients, mostly younger individuals, between the ages of 23 and 46 years, who received the mRNA vaccine and suffered myocarditis [6].

Although reactogenicity or adverse reactions from the COVID-19 vaccines can be expected due to vaccines initiating the physical manifestations of the inflammatory response, these reported local and systemic reactions have created skepticism amongst a certain population that may have even hindered the progress of the mass vaccination efforts globally [7]. Hence the reason why this study analyzed passive surveillance data of reported adverse events gathered from recipients of these US EUA vaccines (Pfizer, Moderna, or Janssen). Information was retrieved from the Vaccine Adverse Event Reporting System (VAERS), a database co-managed by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC). This was assessed to gain further insight into the adverse events experienced by recipients of these vaccines and to know how the ongoing EUA vaccines are faring across the United States [4].

Materials and Methods

Data retrieval

Passive surveillance data recorded for individuals that reported adverse vaccine events after receiving the first or second dose of the COVID-19 Pfizer (Pfizer, New York, NY, USA) or Moderna (Cambridge, MA, USA) vaccines, or the single-dose of Johnson and Johnson vaccine (Johnson & Johnson, New Brunswick, NJ, USA) were retrieved from the VAERS database of the CDC in the United States on July 9, 2021. Records on demographic information such as age and sex as well as the top 10 adverse events reported were accessed. The most common vaccine adverse events were extracted from 200 of the most recently reported cases and populated into an excel spreadsheet. Individuals with incomplete information in the database were excluded from the study selection.

Article selection

An electronic literature search was performed predominantly on PubMed, Google Scholar, and MEDLINE Plus. The search was limited to journals and articles published from July 1, 2019, through August 31, 2021. An article was selected if it was relevant to the topic. Articles were then reviewed and included based on the applicability to the topic.

Data analysis

The data were collected on a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) and frequency distribution for the variables was estimated using percentages. Statistical analyses were conducted using Stata ver. 16.0 (Stata Corp., College Station, TX, USA). Student t-test (for continuous variables), Pearson chi-square tests (for categorical variables where expected cell count ≥5%), Fisher's exact tests (for categorical variables where expected cell count <5%), and one-way analysis of variance for independent variables were used. All tests were two-tailed. All p-values less than 0.05 were considered significant. The level of significance was set at $p<0.05$; therefore, if the probability was lower than the conventional 5%, the result was deemed statistically significant.

Results

Baseline characteristics of VAERS data

Among the 200 evaluated cases, 151 were females, 48 males, and one of unknown sex. In addition, 127 of the 200 cases were between the ages of 12 to 55 years; whereas 73 patients who reported having symptoms were >55 years of age. Each patient was evaluated based on the vaccine received (i.e., Pfizer [n=182], Moderna [n=13], or Janssen [n=5]) along with adverse events reported. Table 1 depicts that fatigue (39.0%), pyrexia (29.5%), headache (35.5%), pain (31.5%), chills (31.5%), arthralgia (14.0%), dizziness (11.0%), nausea (10.0%), peripheral swelling (7.5%), and feeling abnormal (6.0%) were the most common adverse events, with some outcomes occurring concurrently among the cases.

VAERS data stratified by age

Among the 127 recipients in the age group 12 to 55 years, 29

Table 1. Baseline characteristics

Characteristic	Frequency (%)
Gender	
Male	48 (24.0)
Female	151 (75.5)
Unknown	1 (0.5)
Age (yr)	
12–55	127 (63.5)
>55	73 (36.5)
Vaccine	
Pfizer-BioNTech	182 (91.0)
Moderna	13 (6.5)
Janssen	5 (2.5)
Local reaction	17 (8.5)
Erythema at the injection site	1 (5.9)
Pruritus at the injection site	1 (5.9)
Pain at the injection site	10 (58.8)
Reaction at the injection site[a]	5 (29.4)
Systemic reaction: top 10 systemic reaction	200 (100.0)
Fatigue/asthenia	78 (39.0)
Pyrexia/increased body temperature	59 (29.5)
Headache	71 (35.5)
Pain (general)/pain in extremity/myalgia	63 (31.5)
Chills	63 (31.5)
Arthralgia/joint swelling/joint stiffness/joint range of motion decreased/musculoskeletal stiffness	28 (14.0)
Dizziness	22 (11.0)
Nausea	20 (10.0)
Peripheral swelling/eye swelling/face swelling/pharyngeal swelling/oedema/lip swelling/swelling	15 (7.5)
Feeling abnormally/hot or cold	12 (6.0)

Data extracted from the Vaccine Adverse Event Reporting System database [4].
[a]Injection or vaccination site reaction included multiple parameters (i.e., pruritus, pain, swelling, redness, bruising, warmth, irritation, and/or erythema).

were males, 97 were females, and one was of unknown gender. One hundred and sixteen of the 127 of those in the age group 12 to 55 years received the Pfizer vaccine, nine received the Moderna vaccine, and two received the Janssen vaccine. Furthermore, 73 persons were above the age of 55 years, of which 66 received Pfizer's vaccine, four received Moderna vaccine, and three received Janssen vaccine. Local adverse reactions were seen in 13 of the 17 persons in the younger age group, with pain at the injection site being the most frequently reported. Pyrexia, pain, fatigue, headache, and chills were the top five reported systemic reactions among those in the 12 to 55 years age group, whereas those in the >55 years age group reported fatigue, headache, pain, chills, and pyrexia as their top five adverse events, with some outcomes occurring concurrently among the entire patient population as depicted in Table 2. Stratified analysis of the top 10 systemic reactions by age yielded a significant p-value of 0.041 ($p<0.05$).

VAERS data stratified by gender

Table 3 depicts gender: 29 recipients of the vaccines were males between the age of 12 and 55 years, 19 males were above 55 years, 97 vaccine recipients were females between the age of 12 and 55 years, 54 females were above 55 years, and one person of unknown gender was younger than 55 years. Moreover, 42 males received the Pfizer vaccine, two males received Moderna, and four males received Janssen; whereas 139 females received the Pfizer vaccine, 11 females received Moderna vaccine, and one female received Janssen vaccine. The individual of unknown gender received the Pfizer vaccine. Females accounted for the majority of the local adverse reactions reported. Furthermore, the top five reported systemic reactions among males were pain, fatigue, pyrexia, headache, and chills, whereas females had fatigue, headache, chills, pain, and pyrexia, with some outcomes occurring concurrently among the 200 cases. Stratified analysis by gender and vaccine type revealed a non-significant p-value of 0.057 ($p>0.05$) whereas stratification of gender by the top 10 systemic reactions yielded a significant p-value of 0.002 ($p<0.05$).

Top five systemic reactions stratified by the three administered vaccines

Table 4 analyzed five of the most frequently reported systemic adverse reactions among recipients of the three administered vaccines. One hundred and eighty-two people (n=182) who received the Pfizer vaccine reported the following reactions: headache (69 [37.9%]), fatigue (75 [41.2%]), chills (62 [34.1%]), pain (61 [33.5%]), and pyrexia (57 [31.3%]). Thirteen Moderna vaccine recipients (n=13) experienced headache (2 [15.4%]), fatigue (2 [15.4%]), pain (2 [15.4%]), pyrexia (2 [15.4%]), and chills (1 [7.7%]); whereas none of the five Janssen vaccine recipient reported headache, chills, pyrexia, or pain. However, one Janssen recipient experienced fatigue (20.0%). Analysis of the top five systemic adverse reactions by vaccine type yielded a significant p-value of 0.044 for chills ($p<0.05$).

Top five systemic reactions stratified by gender

Table 5 analyzed five of the most frequently reported systemic reactions among the vaccine recipients and the respective

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Table 2. Reported coronavirus disease 2019 vaccine adverse event grouped by age

Characteristic	Age (yr)		p-value
	12–55	>55	
Gender			0.829
Male	29 (22.8)	19 (26.0)	
Female	97 (76.4)	54 (74.0)	
Unknown	1 (0.8)	0	
Vaccine			0.502
Pfizer-BioNTech	116 (91.3)	66 (90.4)	
Moderna	9 (7.1)	4 (5.5)	
Janssen	2 (1.6)	3 (4.1)	
Local reaction	13 (10.2)	4 (5.5)	0.246
Erythema at the injection site	1 (7.7)	0	
Pruritus at the injection site	1 (7.7)	0	
Pain at the injection site	7 (53.8)	3 (75.0)	
Reaction at the injection site[a]	4 (30.8)	1 (25.0)	
Systemic reaction: top 10 systemic reaction			0.041*
Fatigue/asthenia	42 (33.1)	36 (49.3)	
Pyrexia/increased body temperature	44 (34.6)	15 (20.5)	
Headache	43 (33.9)	28 (38.4)	
Pain (general)/pain in extremity/myalgia	44 (34.6)	19 (26.0)	
Chills	43 (33.9)	20 (27.4)	
Arthralgia/joint swelling/joint stiffness/joint range of motion decreased/musculoskeletal stiffness	16 (12.6)	12 (16.4)	
Dizziness	15 (11.8)	7 (9.6)	
Nausea	16 (12.6)	4 (5.5)	
Peripheral swelling/eye swelling/face swelling/pharyngeal swelling/oedema/lip swelling/swelling	11 (8.7)	4 (5.5)	
Feeling abnormally/hot or cold	9 (7.1)	3 (4.1)	

Values are presented as number (%). Data extracted from the Vaccine Adverse Event Reporting System stratified by age [4].
*$p<0.05$ (statistically significant). [a]Injection or vaccination site reaction included multiple parameters (i.e., pruritus, pain, swelling, redness, bruising, warmth, irritation, and/or erythema).

gender. Thirteen of the 42 males who received the Pfizer vaccine experienced a headache (31.0%) and 56 of the 139 females who received the Pfizer vaccine also had a headache (40.3%). Of the two males who received the Moderna vaccine, none of them experienced headache, whereas two females of the 11 who received Moderna did have a headache (18.2%). None of the five Janssen vaccine recipients (four males and one female) experienced any headache. Seventeen of the 42 males who received the Pfizer vaccine complained of fatigue (40.5%), as well as 58 of the 139 females who took the Pfizer vaccine (41.7%). No male recipient of the Moderna vaccine experienced fatigue, although two females of the 11 who received the Moderna vaccine did complain of fatigue (18.2%). The only female patient who received the Janssen vaccine reported having fatigue (100.0%), whereas none of the four males did. Twelve of the 42 males who received the Pfizer vaccine experienced chills (28.6%), and 50 of the 139 females who received the Pfizer vaccine also had chills (36.0%). Of the two male patients who received the Moderna vaccine, none of them experienced chills, whereas one female of the 11 who received the Moderna vaccine had chills (9.1%). None of the five Janssen vaccine recipients (four males and one female) reported having chills. Sixteen of the 42 male patients who received the Pfizer vaccine experienced pyrexia (38.1%), and 40 of the 139 females who received the Pfizer vaccine presented with fever (28.8%). None of the two male patients who received the Moderna vaccine experienced pyrexia, whereas three females of the 11 who received the Moderna vaccine had pyrexia (27.3%). None of the five Janssen vaccine recipients (four males and one female) reported having pyrexia. Nineteen of the 42 male patients who received the Pfizer vaccine experienced pain (45.2%) and 42 of the 139 females who received the Pfizer vaccine complained of pain (30.2%). None of the two male patients who received the Moderna vaccine

Table 3. Reported coronavirus disease 2019 vaccine adverse event grouped by gender

Characteristic	Gender			p-value
	Male	Female	Unknown	
Age (yr)				0.829
12–55	29 (60.4)	97 (64.2)	1 (100.0)	
>55	19 (39.6)	54 (35.8)	0	
Vaccine				0.057
Pfizer-BioNTech	42 (87.5)	139 (92.1)	1 (100.0)	
Moderna	2 (4.2)	11 (7.3)	0	
Janssen	4 (8.3)	1 (0.7)	0	
Local reaction	4 (8.3)	13 (8.6)	0	0.601
Erythema at the injection site	0	1 (0.7)	0	
Pruritus at the injection site	0	1 (0.7)	0	
Pain at the injection site	3 (6.3)	7 (4.6)	0	
Reaction at the injection site[a]	1 (2.1)	4 (2.6)	0	
Systemic reaction: top 10 systemic reaction				0.002*
Fatigue/asthenia	17 (35.4)	61 (40.4)	0	
Pyrexia/increased body temperature	16 (33.3)	43 (28.5)	0	
Headache	13 (27.1)	58 (38.4)	0	
Pain (general)/pain in extremity/myalgia	19 (39.6)	44 (29.1)	0	
Chills	12 (25.0)	51 (33.8)	0	
Arthralgia/joint swelling/joint stiffness/joint range of motion decreased/musculoskeletal stiffness	10 (20.8)	18 (11.9)	0	
Dizziness	4 (8.3)	18 (11.9)	0	
Nausea	3 (6.3)	17 (11.3)	0	
Peripheral swelling/eye swelling/face swelling/pharyngeal swelling/oedema/lip swelling/swelling	0	15 (9.9)	0	
Feeling abnormally/hot or cold	1 (2.1)	11 (7.3)	0	

Values are presented as number (%). Data extracted from the Vaccine Adverse Event Reporting System and stratified by gender [4].
*$p<0.05$ (statistically significant). [a]Injection or vaccination site reaction included multiple parameters (i.e., pruritus, pain, swelling, redness, bruising, warmth, irritation, and/or erythema).

experienced pain, but two of the 11 females who received the Moderna vaccine did experience pain (18.2%). None of the five Janssen vaccine recipients (four males and one female) reported having pain.

Top five systemic reactions stratified by the three administered vaccines and age

Table 6 analyzes five of the most frequently reported systemic adverse reactions among the people who received the vaccines, and their respective age groups. Forty-two of the 116 Pfizer vaccine recipients (n=42) in the age group 12 to 55 years experienced a headache (36.2%), and 27 of the 66 recipients above 55 years of age reported headaches as well (40.9%). One of the nine Moderna vaccine recipients in the age group 12 to 55 years experienced headache (11.1%), as well as one of the four over 55 years of age (25.0%). None of the five Janssen vaccine recipients (two in the 12 to 55 years age group, and three above 55 years) experienced a headache. Thirty-nine of the 116 patients who received Pfizer vaccine (n=39) in the age group 12 to 55 years experienced fatigue (33.6%), as well as 36 of the 66 Pfizer vaccine recipients above age 55 years (54.5%). Two of the nine Moderna vaccine patients in the age group 12 to 55 years experienced fatigue (22.2%), although none of the four patients above 55 years did. One patient of the two who received the Janssen vaccine in the age group 12 to 55 years experienced fatigue (50.0%), whereas none of the three above 55 years of age did. Forty-two of the 116 patients receiving Pfizer (n=42) in the age group 12 to 55 years experienced chills (36.2%), and 20 of the 66 who received Pfizer vaccine above age 55 years did as well (30.3%). One of the nine Moderna vaccine patients in the age group 12 to 55 years experienced chills (11.1%), although none of the four patients above 55 years did. None of the five Janssen patients (two in the 12 to 55 years age group and three above 55 years) reported chills. Forty-four of the 116 male patients who received Pfizer vaccine (n=44) in the age

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Table 4. Top five systemic reactions stratified by the three administered vaccines

	Vaccines			Total	p-value
	Pfizer	Moderna	Janssen		
Headache					0.064
No	113	11	5	129	
Yes	69	2	0	71	
Total	182	13	5	200	
Fatigue[a]					0.124
No	107	11	4	122	
Yes	75	2	1	78	
Total	182	13	5	200	
Chills					0.044*
No	120	12	5	137	
Yes	62	1	0	63	
Total	182	13	5	200	
Pyrexia[b]					0.165
No	125	11	5	141	
Yes	57	2	0	59	
Total	182	13	5	200	
Pain[c]					
No	121	11	5	137	0.123
Yes	61	2	0	63	
Total	182	13	5	200	

Data extracted from the Vaccine Adverse Event Reporting System database [4]. *$p<0.05$ (statistically significant). [a]Fatigue and asthenia. [b]Pyrexia and increased body temperature. [c]Pain, pain in extremity, and myalgia grouped together.

group 12 to 55 years experienced pyrexia (37.9%), and 13 of the 66 who received Pfizer vaccine above 55 years presented with fever (19.7%). None of the nine patients in the 12 to 55 years age group who received Moderna vaccine experienced pyrexia, although two of the four above 55 years of age who received Moderna vaccine did (50.0%). None of the five Janssen patients (two in the 12 to 55 years age group and three above 55 years) reported pyrexia. Forty-two of the 116 patients who received Pfizer vaccine (n=42) in the age group 12 to 55 years experienced pain (36.2%) and 19 of the 66 who received Pfizer vaccine above 55 years of age did as well (28.8%). Two of the nine Moderna vaccine recipients in the age group 12 to 55 years experienced pain (22.2%), although none of the four people above 55 years of age did. None of the five Janssen patients (two in the 12 to 55 years age group and three above 55 years) reported having pain. Analysis of the top five systemic reactions stratified by age and vaccine type yielded a significant p-value of 0.023 ($p<0.05$) and a non-significant p-value of 0.051 ($p>0.05$) for fatigue and pyrexia, respectively.

Discussion

Currently, there are 12 vaccines recognized and approved for use by the US FDA, the World Health Organization (WHO), and the European Medicines Agency, with 66 other prospective COVID-19 vaccines in various stages of clinical trials around the world [8]. Despite having larger percentages of systemic adverse effects, currently, the Pfizer vaccine has the highest efficacy rate (95.0%) of the 12 approved vaccines, with 54 countries approving its use based on seven trials in eight countries [8]. The Moderna vaccine has a slightly lesser efficacy rate (94.5%) than the Pfizer vaccine and is approved in 37 countries after five trials in one country [8]. The Janssen vaccine, despite having reportedly lower efficacy rates (73.1% against severe disease, and 81.7% against critical disease), has been approved in 53 countries after 11 trials in seven different countries [8]. By June 14, 2021, the CDC documented over 3,500 reports of side effects in the United States by some people who received a COVID-19 vaccine [8].

Tables 1–6 retrospectively analyzed surveillance data on adverse events related to the three COVID-19 vaccines, i.e., Pfizer-BioNTech, Moderna, and Janssen given in the United States. Several symptoms reported in the VAERS database (i.e., headache, fatigue, chills, pyrexia, and pain) were assessed concerning the identified gender and two age groups (those 12 to 55 years of age and those greater than 55 years). Table 1 presented the most common adverse events related to these vaccines which consisted of fatigue (39.0%), headache (35.5%), pain (31.5%), chills (31.5%), pyrexia (29.5%), arthralgia (14.0%), dizziness (11.0%), nausea (10.0%), peripheral swelling (7.5%), and feeling abnormal (6.0%). Furthermore, only 17 people (8.5%) out of 200 vaccine recipients reported local adverse events, with 10 of the 17 (58.8%) reporting pain at the injection site as the most common complaint. In a clinical trials study of the two mRNA-based vaccines, Pfizer-BioNTech and Moderna, recipients reported reactogenicity, including local and systemic reactions, from day 0 to day 7 after vaccination [9]. The most reported responses, based on compiled information from Chapin-Bardales et al. [9], after the first dose of both vaccines, were injection site pain (67.8%), fatigue (30.9%), headache (25.9%), and myalgia (19.4%). The second dose of both vaccines produced significantly greater reactogenicity, especially systemic reactions, including fatigue (53.9%), headache (46.7%), myalgia (44.0%), chills (31.3%), fever (29.5%), and joint pain (25.6%) [9]. On January 29, 2021, Johnson and Johnson reported that the

Table 5. Top five systemic reactions stratified by gender

	Vaccines by gender							Total	p-value
	Pfizer (n=182)			Moderna (n=13)		Janssen (n=5)			
	Male	Female	Unknown	Male	Female	Male	Female		
Headache									0.111
No	29	83	1	2	9	4	1	129	
Yes	13	56	0	0	2	0	0	71	
Total	42	139	1	2	11	4	1	200	
Fatigue[a]									0.274
No	25	81	1	2	9	4	0	122	
Yes	17	58	0	0	2	0	1	78	
Total	42	139	1	2	11	4	1	200	
Chills									0.105
No	30	89	1	2	10	4	1	137	
Yes	12	50	0	0	1	0	0	63	
Total	42	139	1	2	11	4	1	200	
Pyrexia[b]									0.297
No	26	99	1	2	8	4	1	141	
Yes	16	40	0	0	3	0	0	59	
Total	42	139	1	2	11	4	1	200	
Pain[c]									0.113
No	23	97	1	2	9	4	1	137	
Yes	19	42	0	0	2	0	0	63	
Total	42	139	1	2	11	4	1	200	

Data extracted from the Vaccine Adverse Event Reporting System database [4].
[a]Fatigue and asthenia. [b]Pyrexia and increased body temperature. [c]Pain, pain in extremity, and myalgia grouped together.

Janssen vaccine; a single dose, viral vector vaccine, is 72.0% effective at preventing COVID-19 in the United States, and 66.0% effective at preventing moderate to severe COVID-19 [10], with most people developing immunity 2 weeks after receiving the vaccine [11]. Throughout clinical trials, mild side effects were more prevalent in people aged 18 to 59 years and detected during the first 7 days [11]. The most common local side effects reported included pain at the injection site (48.6%), whereas the most common systemic side effects were fatigue (38.2%), headache (38.9%), and muscle pain (33.2%) [11]. These results are not surprising because such adverse events occur at high frequencies with all vaccines, not just the COVID-19 vaccines [12].

Perhaps the reason why several governments and agencies (including the CDC, WHO, and the Government of Canada) agree that all individuals who are eligible to receive the vaccine should get vaccinated [13-15]. In the clinical trial above, a significant percentage of Moderna vaccine recipients reported reactogenicity compared with the Pfizer-BioNTech vaccine [9]. Recipients aged 65 years and older reported local and systemic reactions less frequently than those younger than 65 years; both age groups demonstrated greater reactogenicity after the second dose [9]. In addition, both doses of both vaccines yielded the highest number of local and systemic reactions on day 1 after vaccination, with the number of responses decreasing markedly through day 7 [9].

A further look into the data obtained from VAERS, as shown in Table 2, indicated that local adverse events seem to occur more in the 12- to the 55-year-old age group; however, one of the limitations of the study is the larger number of people in the 12- to the 55-year-old age group that received the vaccine (127 vaccine recipients) as compared to those >55 years of age (73 vaccine recipients). As per the systemic reactions, as shown in Table 5, some recipients of the three vaccines (Pfizer, Moderna, and Janssen) had systemic reactions to some degree; with fatigue being the most common as reported by 75 of the 182 people who received Pfizer vaccine, two of the 13 people who received Moderna vaccine and one of the five people who received Janssen vaccine.

A closer look at age groups in one study revealed that 88.7%

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Table 6. Top five systemic reactions stratified by the three administered vaccines and age

	Vaccines by age (yr)						Total	p-value
	Pfizer (n=182)		Moderna (n=13)		Janssen (n=5)			
	12–55	>55	12–55	>55	12–55	>55		
Headache								0.110
No	74	39	8	3	2	3	129	
Yes	42	27	1	1	0	0	71	
Total	116	66	9	4	2	3	200	
Fatigue[a]								0.023*
No	77	30	7	4	1	3	122	
Yes	39	36	2	0	1	0	78	
Total	116	66	9	4	2	3	200	
Chills								0.070
No	74	46	8	4	2	3	137	
Yes	42	20	1	0	0	0	63	
Total	116	66	9	4	2	3	200	
Pyrexia[b]								0.051
No	72	53	9	2	2	3	141	
Yes	44	13	0	2	0	0	59	
Total	116	66	9	4	2	3	200	
Pain[c]								0.133
No	74	47	7	4	2	3	137	
Yes	42	19	2	0	0	0	63	
Total	116	66	9	4	2	3	200	

Data extracted from the Vaccine Adverse Event Reporting System database [4].
*$p<0.05$ (statistically significant). [a]Fatigue and asthenia. [b]Pyrexia and increased body temperature. [c]Pain, pain in extremity, and myalgia grouped together.

of vaccine recipients aged 18 to 55 years and 79.7% of vaccine recipients >55 years of age reported at least one localized reaction after receiving the Pfizer-BioNTech mRNA-based vaccine [16]. The most prevalent and severe local reaction was injection site pain, with those aged 18 to 55 years reporting having pain after the first dose (83.1%) and after the second dose (77.8%), as compared to vaccine recipients 55 years and older (71.1% after the first dose and 66.8% after the second dose) [16]. Reactogenicity data for local adverse reactions from adolescents aged 12 to 15 years were comparable to those of adults aged 18 to 55 years [16]. Data on local reactions from recipients aged 16 to 17 years were estimated to be equivalent to that of the adolescent age group [16]. These results were similar to our results; although our study did not assess the number of doses received.

Among all the Pfizer-BioNTech mRNA-based vaccine recipients, 77.4% reported having systemic reactions, with those aged 18 to 55 years experiencing higher reactogenicity compared to the recipients >55 years [16]. After both doses of the Pfizer-BioNTech mRNA-based vaccine, most of the systemic events recorded were mild to moderate, with fatigue, headache, and muscle pain being the most prevalent in both age groups [16]. The probability of a systemic reaction increased after the second dose for both age groups; however, 15.8% of patients aged 18 to 55 years experienced fever as the most common systemic effect after the second dose compared to only 10.9% of the patients >55 years [16].

Both males and females who received the Pfizer vaccine in our study experienced all five systemic reactions to some degree. Male recipients of the Moderna vaccine seemed to experience fewer systemic side effects than their female counterparts. Both the males and females who received the Janssen vaccine seemed to experience fewer systemic reactions. As seen in Table 2 stratification by age and systemic reactions yielded a significant difference between the two age groups. While stratification by gender and vaccine type yielded no significant value, systemic reactions stratified by gender revealed a significant difference between the two sexes as depicted in Table 3.

The analysis of the top five systemic reactions by vaccine

type yielded a significant difference for chills as seen in Table 4. Further stratification in Table 6 shows that the analysis of the top five systemic reactions stratified by age and vaccine type yielded a significant difference for fatigue across the different age groups and vaccination types received. Fatigue and chills are among the top mentioned systemic reactions in other studies [9,11]. Although, there is a lack of sufficient data; the lower rate of systemic adverse events experienced by those who received the Janssen vaccine, could be attributed to the adenovirus viral vector triggering a slightly different immunologic response in certain patients due to its biological nature as compared to the mRNA derived Pfizer and Moderna vaccines. Mild side effects have been reported by recipients of the Janssen vaccine [11].

Although our study did not report on other adverse reactions like allergic reactions, facial paralysis, myocarditis, pericarditis, and venous thromboembolic episodes; these events were reported in other studies [17-21]. In one study, approximately 98.0% of recipients did not have any allergic reaction to vaccination [17,18]. The remaining 2.0% of Pfizer-BioNTech and Moderna vaccine recipients reported having some allergy symptoms [17,18]. Severe reactions consistent with anaphylaxis occurred at a rate of 2.47 per 10,000 vaccinations [17,18]. All recipients with anaphylaxis recovered without endotracheal intubation or shock [17,18]. The people who did experience anaphylactic reactions after receiving an mRNA-based COVID-19 vaccine also had a history of allergies, with 31.0% of recipients having a history of prior anaphylaxis [17,18]. Despite this response, most recipients of these vaccines who have allergy histories did not have any acute allergic reactions [17,18]. Hence, the overall risk of an acute allergic reaction to an mRNA COVID-19 vaccine is minimal and is comparable to other common healthcare exposures [17,18]. Unfortunately, there have also been reports of patients in a vaccine group developing facial paralysis during phase 3 of the clinical trials (seven of 35,654) [19]. However, as reported in the study by Renoud et al. [19], the rate of facial paralysis was not higher in mRNA COVID-19 vaccines when compared with other viral vaccines. Therefore, the FDA currently recommends monitoring for facial paralysis [19]. Furthermore, as concluded by Renoud et al. [19], despite no apparent connection between mRNA COVID-19 vaccines and facial paralysis, if any exists it will be minimal.

In another study, although there were no anaphylactic reactions during vaccine administration, one hypersensitivity reaction was reported [20]. During the trials with 43,783 patients, those who received the vaccine experienced significantly more venous thromboembolic episodes (N=11) such as deep vein thrombosis, pulmonary emboli, and transverse venous sinus thrombosis than those who received a placebo (N=3) [20]. After reports of six US cases of CVST and more cases of thrombosis with thrombocytopenia (TTS) being reported, on April 13, 2021, the CDC and FDA halted the use of the Janssen COVID-19 vaccine for 10 days [22]. In contrast, there have not been any reports of either of the mRNA COVID-19 vaccines being associated with CVST or TTS in its recipients after either dose [22]. On April 23, 2021, both the CDC and FDA advised resuming the use of the Janssen vaccine in the United States [10] as well as recommending counseling women under the age of 50 years about the possible risk of developing rare blood clots and possible platelet destruction [11]. The decision to resume its use came after careful consideration of the protection provided by the vaccine and the volume of lives it could save worldwide, which surpasses the dangers of the possibility of TTS. Many of the cases identified were among women aged 18 to 49 years [22].

Incidences of myocarditis and pericarditis were observed after COVID-19 vaccination in a study. Myocarditis developed rapidly in younger patients, mainly after the second vaccination. While pericarditis affected older patients later, after either the first or second dose [21].

Assessing reactogenicity and safety of vaccines are important measures when considering the global use of a vaccine. However, what is arguable of utmost importance is the efficacy; there needs to be concrete evidence that the vaccine will protect against COVID-19. Determining efficacy is complex when looking at it in the context of a novel virus. According to Hodgson et al. [23], the most important efficacy endpoint is reducing mortality and severe disease, due to the burden placed on healthcare systems. The phase 3 clinical trial that was conducted to determine the efficacy of the Pfizer-BioNTech vaccine randomized 43,448 volunteers to receive either the vaccine or a placebo [2]. The trial results showed that the Pfizer-BioNTech vaccine is 95.0% effective at preventing COVID-19, and the trial did not identify any safety concerns [2]. The phase 3 trial that was conducted to determine the efficacy of the Moderna vaccine randomized 30,420 volunteers to receive either the vaccine or a placebo [24]. The trial results showed that the Moderna vaccine is 94.1% effective at preventing COVID-19, and the trial did not identify any safety concerns [24]. Lastly, the phase 3 trial that was conducted to determine the efficacy of the Janssen vaccine randomized

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43,784 volunteers to receive either the vaccine or a placebo [25]. The trial results revealed that the vaccine is 66.9% effective at preventing COVID-19 [25].

RNA viruses, including SARS-CoV-2, are prone to genetic evolution while adapting to their hosts and thus, develop new mutations over time, resulting in new strains [26]. Since the start of the pandemic, new strains have been spreading rapidly. Therefore, vaccines should also be effective against these new emerging strains [27]. The alpha (B.1.1.7), beta (B.1.351), delta (B1.617.2), and gamma (P.1) are the strains of SARS-CoV-2 that are of interest in the United States [26,27]. An observational cohort study showed that the Pfizer-BioNTech vaccine was effective against the alpha (87.0%) and beta (75.0%) strains [28]. Clinical trials for vaccines against the other variants of interest are still ongoing. The efficacy of the Moderna and Janssen vaccines against these variants of interest is currently unknown [26]. Despite the rapid production and development of these vaccines, worldwide vaccination efforts may be threatened by the emergence of new variants.

Recently there has been increasing discussion regarding the efficacy of current vaccines to prevail against new variants of the virus, such as the B.1.1.7 variant (α variant; WHO classification) and the B.1.351 variant (β variant; WHO classification) [8]. While it's still early to determine, a study in Qatar carried out by Abu-Raddad et al. [28], reported that patients who were given the standard two doses of the Pfizer-BioNTech vaccine had lower chances of developing COVID-19 from the B.1.351 (β) variant (75.0%) as compared to patients who were unvaccinated [8].

Due to the novelty of the virus, there is still a lot that remains to be ascertained. Many have wondered whether the vaccines prevent transmission of the virus and whether a booster dose will be required. Recently released non-peer-reviewed articles have suggested that individuals who have received both doses of the Pfizer-BioNTech and the Moderna vaccines are less likely to transmit the virus to others, and they are less likely to have asymptomatic infections [29,30]. There are additional studies currently underway to confirm these conclusions. Likewise, it is still unknown how long the immunity due to the vaccines would last and whether they will be needed for a booster dose. Determining an established immune response to the COVID-19 vaccine depends on the detection of SARS-CoV-2 specific immunoglobulin G (IgG) antibodies [31]. Some studies have suggested the rapid decline of these IgG antibodies, suggesting that a booster dose may be needed to maintain immunity; however, the rate of decline was not detailed [32,33]. Those who received the Pfizer and Moderna vaccine could be eligible for booster doses 8 months after receiving the second dose according to the CDC [34].

In conclusion, SARS-CoV-2 has infected millions of people across multiple nations all over the world and continues to do so while wreaking havoc and chaos. This is partially due to SARS-CoV-2 having specialized viral proteins that make it much more elusive to the body's immune system and causing it to be destructive to the human host. In addition to therapeutics, vaccines were produced to limit transmissibility and mortality; however, due to the EUA, the lack of historical data made it difficult to accurately predict adverse events. Some frequent reactions such as fatigue, pyrexia, and headache were reported as adverse effects shared among Pfizer-BioNTech, Moderna, and Janssen vaccines. Due to the novelty of the virus, there are still many unanswered questions regarding these vaccines' long-term reactogenicity. Additional independent studies on the efficacy and safety of these vaccines are strongly recommended to strengthen public confidence regarding COVID-19 vaccines, in addition, to ascertain all potential risk factors associated with each vaccine's adverse reactions. People are encouraged to take any of the vaccines to assist in fighting and defeating the virus. It is noted that the benefits of taking the vaccines far outweigh the risk of contracting COVID-19 and perhaps, dying from it. We implore well-meaning individuals, community groups, government agencies, non-governmental organizations, religious groups, and so forth. to encourage their patrons and members to take any of the vaccines to achieve herd immunity and end the pandemic.

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