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Reactogenicity within 2 weeks after mRNA COVID-19 vaccines: Findings from the CDC v-safe surveillance system

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ABSTRACT

Background: Post-authorization monitoring of mRNA-based COVID-19 vaccines is needed to better characterize their reactogenicity. We assessed reactions reported during the 2 weeks after receipt of BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) vaccines.

Methods: We monitored persons who enrolled in *v-safe after vaccination health checker*SM, a U.S. smartphone-based vaccine monitoring system, after receiving BNT162b2 or mRNA-1273. V-safe participants received text message prompts to complete web-based surveys. We analyzed responses from persons who received BNT162b2 or mRNA-1273 from December 14, 2020 through March 14, 2021 and completed at least one survey by March 28, 2021. We measured the proportion of participants reporting local and systemic reactions solicited in surveys completed days 0 through 7 post-vaccination. For day 14 surveys, participants described new or worsening symptoms in a free-text response. We assessed the proportion of participants reporting new or worsening local and systemic reactions.

Results: One-third of participants were aged <45 years, two-thirds were female, and approximately half received BNT162b2 vaccine. A total of 4,717,908 participants reported during the 7 days after dose 1 and 2,906,377 reported during the 7 days after dose 2. Most reported at least one injection-site reaction (68.5% after dose 1; 72.9% after dose 2) or at least one systemic reaction (50.6% after dose 1; 69.5% after dose 2). Reactogenicity was greater after dose 2 and among mRNA-1273 recipients, persons aged <45 years, and females. New or worsening local and systemic reactions were uncommon during week 2 after either dose; the most frequent were local reactions for dose 1 mRNA-1273 recipients (2.6%). These reactions were reported more often among females after dose 1 mRNA-1273 (3.6%).

Conclusions: During post-authorization monitoring among >4 million vaccinees, local and systemic reactions were commonly reported following mRNA-based vaccines. Reactions were most common during the first week following dose 2 and among persons aged <45 years, females, and mRNA-1273 recipients.

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1. Introduction

In December 2020, two mRNA-based COVID-19 vaccines were granted Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration and recommended for use by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention [1,2]. Commonly reported local and systemic reactions in clinical trials of BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) COVID-19 vaccines included injection site pain, fatigue, and headache; these were more frequently reported after dose 2 for both vaccines [3,4]. Clinical trials also found differences by age, with younger participants reporting greater reactogenicity [3,4].

Monitoring reactogenicity of COVID-19 vaccines during the post-authorization period is important to better characterize the safety profiles of these vaccines, including among recipients in larger, more diverse populations. The novel mRNA-based technology of these vaccines also requires further assessment of reactogenicity in vaccine recipients. CDC established the *v-safe after vaccination health checker*SM (herein referred to as v-safe), a smartphone-based active surveillance system in the United States to gather additional information on reactogenicity of COVID-19 vaccines [5]. Initial analyses of v-safe data indicated that injection site pain, fatigue, headache, myalgia, and chills were commonly reported

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after receipt of mRNA-based COVID-19 vaccines, especially following dose 2, and were most frequent the day after vaccination [6,7].

Delayed injection site reactions occurring after 7 days post-vaccination were reported in the mRNA-1273 clinical trial, although they were uncommon [4]. During the first two months of the U.S. COVID-19 vaccination program, healthcare providers offered anecdotal reports of unusual injection site reactions during the second week post-vaccination [8]. In some media reports, these reactions were described as "COVID arm" [9]. Published reports have described a delayed-type hypersensitivity reactions among mRNA-1273 vaccine recipients who noted redness, pain, itching, swelling, and rash near the injection site, with a median onset on day 8 after dose 1 [10,11].

We aimed to assess local and systemic reactions during the week following mRNA-based COVID-19 vaccination among v-safe participants and identify any differences by dose, vaccine product, and vaccine recipient characteristics. In addition, we hypothesized that injection site reactions may be reported to v-safe in the second week following vaccination. We therefore evaluated local and systemic reactions reported up to two weeks after each vaccine dose.

2. Material and methods

2.1. V-safe after vaccination health checker^{SM} surveillance system

V-safe participants self-enroll and provide the system with information about the COVID-19 vaccine received, demographics, and smartphone number. Following enrollment, participants receive text messages that prompt them to begin web-based health surveys at specific intervals (see Supplemental Material—Section A). The full v-safe protocol is publicly available [5]. Participants receive daily health surveys on days 0 (day of vaccination) through 7 after each vaccine dose. Daily surveys include specific questions about local reactions (injection site pain, redness, swelling, and itching) and systemic reactions (fatigue, headache, muscle and body aches [myalgia], chills, fever, joint pain, nausea, vomiting, diarrhea, abdominal pain, and rash outside the injection site). Participants are asked about reactions they experienced "today" on the specific day the survey was completed. Surveys for days 0–6 following vaccination can only be completed the day of the corresponding text message is received. Like other surveys, the day 7 survey can only be completed once; however, a participant can complete this survey during days 7–13 following a given vaccine dose. For our main analysis, we only included those who completed the day 7 survey on day 7 for consistency with data evaluated in clinical trials [3,4]. A subanalysis of day 7 surveys completed on days 8 to 13 was conducted and presented separately.

Weekly surveys beginning at week 2 (day 14) post-vaccination do not include specific questions about solicited local and systemic reactions. Rather, weekly surveys include a question about whether the participant experienced any "new or worsening symptoms or health conditions" since the participant's last completed survey; if yes, participants are asked to enter up to 250 characters of free-text data to describe their new or worsening symptoms. The day 14 survey can be completed from days 14 through 20 following a vaccine dose. We restricted analysis of day 14 surveys to participants who answered on day 14 after vaccination to focus specifically on the second week after each vaccine dose.

2.2. Data analysis

All analyses were restricted to participants who received a COVID-19 vaccine dose from December 14, 2020 through March 14, 2021. Follow-up continued through March 28, 2021 to allow a 14-day reporting period after the day of vaccination. SAS 9.4 (SAS Institute Inc., Cary, NC) was used to perform data analysis and R's ggplot2 package was used to create figures. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy (see e.g., 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq).

2.3. Outcomes on days 0–7 following vaccination

We conducted descriptive analyses of solicited (e.g., pre-specified) local and systemic reactions during the first week after vaccination. Numerators for these analyses were numbers of persons who reported a given solicited reaction during days 0 to 7 following the respective vaccine dose. Denominators were numbers of persons who completed at least one survey during days 0 to 7. The number and percentage of participants reporting solicited reactions were evaluated by vaccine dose and product overall and by age (<45 years, 45–54 years, 55–64 years, and $\geq$ 65 years) and sex (female, male, other).

2.4. Outcomes on day 14 following vaccination

Free-text responses from participants who reported new or worsening symptoms on day 14 post-vaccination (dose 1 n = 171,003; dose 2 n = 74,603) were analyzed using text search methods in SAS (e.g., prx functions) [12]. Detailed methods are described in the Supplemental Material—Section B. In brief, to align free-text responses on the day 14 surveys with the local and systemic reactions solicited in day 0 to 7 surveys, we created a list of key terms to define each reaction (e.g., injection site pain, fatigue, headache). Special characters and spaces were removed from text strings prior to the case-insensitive search; for some key terms that could be common roots for words unrelated to the reaction of interest (e.g. "red"), the unmodified text string with spaces was used and a word boundary rule was applied (i.e., a non-word character or beginning or ending of the string was required before and after the key term). We created binary variables for each reaction using text search functions.

We then conducted a key term refinement process. We generated a random sample of 500 participants who provided free-text responses (250 from the dose 1, day 14 survey and 250 from the dose 2, day 14 survey). We performed a manual review of the text responses, which assigned values (yes/no) for the presence of each outcome of interest based on each text response. We then created corresponding binary variables for each reaction based on the manual review. The variables created via text search methods and the variables created via manual review were then compared and measures of validity (i.e., sensitivity, specificity, positive predictive value, negative predictive value, and accuracy) were calculated. Records classified as false positive or false negative were reviewed to determine potential refinements to the search terms; identified refinements were then applied to the text search terms. After this refinement process, we performed manual review of a second random sample of 500 text responses (250 from dose 1, day 14 survey and 250 from dose 2, day 14 survey) and then reassessed validity of measures when applying the refined text search terms. Validity of measures increased substantially after refinement of the key terms (Supplemental Material—Section B); thus no further refinement was conducted. For the main analyses, variables created via the refined text search functions were then modified to include participants that reported not having any new or worsening symptoms as not having the given reaction assessed. The number and percentage of participants reporting a given reaction among those that completed the day 14 survey after a respective vaccine dose were then calculated.

3. Results

3.1. Participant characteristics

Characteristics of v-safe participants receiving an mRNA-based COVID-19 vaccine by March 14, 2021 and completing at least one survey through March 28, 2021 are described in Table 1. One-third of participants were aged <45 years and another third were ≥65 years; two-thirds of participants were female, and approximately half of participants received the BNT162b2 vaccine. Sex distributions were similar by vaccine product. Recipients of BNT162b2 vaccine were younger; this pattern was consistent across survey day periods and doses.

3.2. Outcomes on days 0–7 following vaccination

A total of 4,717,908 v-safe participants reported receiving dose 1 of an mRNA-based COVID-19 vaccine and completed at least one survey during days 0 to 7 following dose 1. Of these, 47.2% received the BNT162b2 and 52.8% mRNA-1273. A total of 2,906,377 participants reported receiving dose 2 of an mRNA-based vaccine and completed at least one survey during days 0 to 7 following dose 2 (46.7% BNT162b2 and 53.3% mRNA-1273).

A majority of participants reported at least one injection site reaction (68.5% after dose 1; 72.9% after dose 2) or at least one systemic reaction (50.6% after dose 1; 69.5% after dose 2) (Table 2). The percentage of participants reporting injection sites reactions after dose 2, compared with dose 1, was slightly higher; for systemic reactions, reports after dose 2 were substantially higher. The most common reactions after dose 1 were injection site pain (66.3%), fatigue (31.7%), headache (25.9%), and myalgia (19.5%). After dose 2, injection site pain (69.7%), fatigue (53.9%), headache (45.5%), myalgia (43.0%), chills (30.4%), fever (28.8%), joint pain (25.1%), injection site swelling (17.7%), and nausea (15.6%) were commonly reported. Participants who received the mRNA-1273 vaccine, compared with the BNT162b2 vaccine, reported greater reactogenicity, particularly after dose 2. After dose 2, 75.4% of mRNA-1273 recipients vs. 63.2% of BNT162b2 recipients reported injection site pain, 59.6% vs. 47.3% reported fatigue, and 51.3% vs. 38.9% reported headache.

These patterns, including greater reactogenicity after the second dose and among mRNA-1273 recipients, were consistent by reaction type, age group, and sex (Fig. 1). Reactogenicity was highest among persons aged <45 years and gradually declined with increasing age; persons 65 years and older reported the least reactogenicity. A greater percentage of females, compared with males, reported reactions; this pattern was consistent by reaction type, vaccine dose, and vaccine product.

Results from the subanalysis of day 7 surveys completed on days 8 to 13 are presented in the Supplemental Material—Section C.

3.3. Outcomes on day 14 following vaccination

A total of 3,311,931 participants reported receiving dose 1 of an mRNA-based vaccine and completed the day 14 survey on day 14 after dose 1 (47.5% BNT162b2 and 52.5% mRNA-1273). A total of 2,252,809 reported receiving dose 2 of an mRNA-based vaccine

Table 1
Characteristics of v-safe participants receiving mRNA COVID-19 vaccines—CDC v-safe surveillance system, December 14, 2021 through March 28, 2021.

	Both vaccines				BNT162b2				mRNA-1273			
	Dose 1		Dose 2		Dose 1		Dose 2		Dose 1		Dose 2	
	n	%	n	%	n	%	n	%	n	%	n	%
DAYS 0 to 7	**4,717,908**		**2,906,377**		**2,228,912**		**1,358,338**		**2,488,996**		**1,548,039**	
Manufacturer												
BNT162b2	2,228,912	47.2	1,358,338	46.7	–	–	–	–	–	–	–	–
mRNA-1273	2,488,996	52.8	1,548,039	53.3	–	–	–	–	–	–	–	–
Age (years)[1]												
<45	1,611,995	34.2	986,563	33.9	805,574	36.1	488,387	36.0	806,421	32.4	498,176	32.2
45–54	793,744	16.8	488,198	16.8	381,381	17.1	230,054	16.9	412,363	16.6	258,144	16.7
55–64	848,197	18.0	479,239	16.5	400,401	18.0	220,828	16.3	447,796	18.0	258,411	16.7
≥65	1,463,963	31.0	952,372	32.8	641,553	28.8	419,068	30.9	822,410	33.0	533,304	34.5
Not reported	9	–	5	–	3	–	1	–	6	–	4	–
Sex[1]												
Female	3,027,171	64.9	1,949,437	68.0	1,437,018	65.2	913,978	68.2	1,590,153	64.6	1,035,459	67.8
Male	1,633,261	35.0	917,573	32.0	765,394	34.7	426,081	31.8	867,867	35.3	491,492	32.2
Other	3,250	0.1	1,772	0.1	1,505	0.1	764	0.1	1,745	0.1	1,008	0.1
Not reported	54,226	–	37,595	–	24,995	–	17,515	–	29,231	–	20,080	–
DAY 14	**3,311,931**		**2,252,809**		**1,573,710**		**1,061,536**		**1,738,221**		**1,191,273**	
Manufacturer												
BNT162b2	1,573,710	47.5	1,061,536	47.1	–	–	–	–	–	–	–	–
mRNA-1273	1,738,221	52.5	1,191,273	52.9	–	–	–	–	–	–	–	–
Age (years)[1]												
<45	1,013,398	30.6	687,933	30.5	512,245	32.6	345,512	32.5	501,153	28.8	342,421	28.7
45–54	569,946	17.2	387,929	17.2	276,957	17.6	184,937	17.4	292,989	16.9	202,992	17.0
55–64	635,961	19.2	397,383	17.6	303,279	19.3	184,844	17.4	332,682	19.1	212,539	17.8
≥65	1,092,620	33.0	779,561	34.6	481,227	30.6	346,243	32.6	611,393	35.2	433,318	36.4
Not reported	6	–	3	–	2	–	0	–	4	–	3	–
Sex[1]												
Female	2,135,017	65.1	1,493,617	67.1	1,015,915	65.2	706,776	67.4	1,119,102	65.1	786,841	66.9
Male	1,139,944	34.8	730,530	32.8	540,645	34.7	341,337	32.5	599,299	34.9	389,193	33.1
Other	2,139	0.1	1,283	0.1	994	0.1	581	0.1	1,145	0.1	702	0.1
Not reported	34,831	–	27,379	–	16,156	–	12,842	–	18,675	–	14,537	–

Abbreviations: COVID-19 = coronavirus disease 2019.
[1]'Not reported' categories are presented for clarity but not included in calculation of column percentages for the respective variable.

Table 2
Number and percentage of v-safe participants reporting local and systemic reactions to mRNA COVID-19 vaccines at least once during days 0 to 7 following vaccination—CDC v-safe surveillance system, December 14, 2021 through March 28, 2021.

	Both vaccines				BNT162b2				mRNA-1273			
	Dose 1 (N = 4,717,908)		Dose 2 (N = 2,906,377)		Dose 1 (N = 2,228,912)		Dose 2 (N = 1,358,338)		Dose 1 (N = 2,488,996)		Dose 2 (N = 1,548,039)	
	n	%	n	%	n	%	n	%	n	%	n	%
Any injection site reaction[1]	3,232,906	68.5	2,118,006	72.9	1,417,891	63.6	891,230	65.6	1,815,015	72.9	1,226,776	79.2
Injection site pain	3,126,740	66.3	2,025,391	69.7	1,374,942	61.7	858,862	63.2	1,751,798	70.4	1,166,529	75.4
Injection site redness	254,587	5.4	355,676	12.2	74,344	3.3	78,063	5.8	180,243	7.2	277,613	17.9
Injection site swelling	482,038	10.2	515,157	17.7	148,018	6.6	136,189	10.0	334,020	13.4	378,968	24.5
Injection site itching	254,892	5.4	327,548	11.3	86,136	3.9	85,400	6.3	168,756	6.8	242,148	15.6
Any systemic reaction[2]	2,386,117	50.6	2,020,650	69.5	1,085,168	48.7	863,699	63.6	1,300,949	52.3	1,156,951	74.7
Fatigue	1,494,013	31.7	1,565,506	53.9	668,670	30.0	642,474	47.3	825,343	33.2	923,032	59.6
Headache	1,222,104	25.9	1,322,554	45.5	548,946	24.6	528,773	38.9	673,158	27.0	793,781	51.3
Myalgia	919,505	19.5	1,249,698	43.0	382,292	17.2	479,935	35.3	537,213	21.6	769,763	49.7
Chills	418,863	8.9	882,228	30.4	158,339	7.1	293,110	21.6	260,524	10.5	589,118	38.1
Fever	410,792	8.7	837,459	28.8	158,656	7.1	278,723	20.5	252,136	10.1	558,736	36.1
Joint Pain	418,651	8.9	729,793	25.1	169,959	7.6	260,509	19.2	248,692	10.0	469,284	30.3
Nausea	358,844	7.6	454,135	15.6	154,760	6.9	167,578	12.3	204,084	8.2	286,557	18.5
Vomiting	33,597	0.7	44,343	1.5	13,731	0.6	14,973	1.1	19,866	0.8	29,370	1.9
Diarrhea	251,792	5.3	202,092	7.0	115,079	5.2	84,392	6.2	136,713	5.5	117,700	7.6
Abdominal Pain	146,235	3.1	171,287	5.9	64,748	2.9	65,109	4.8	81,487	3.3	106,178	6.9
Rash outside of injection site	56,266	1.2	49,775	1.7	24,806	1.1	18,446	1.4	31,460	1.3	31,329	2.0

Abbreviations: COVID-19 = coronavirus disease 2019.
[1]**Any** of the listed injection site reactions.
[2]**Any** of the listed systemic reactions.

and completed the day 14 survey on day 14 after dose 2 (47.1% BNT162b2 and 52.9% mRNA-1273).

Overall, the proportion of participants reporting new or worsening injection site reactions and systemic reactions assessed on the day 14 survey was low after either first or second doses (Table 3). Injection site reactions were most frequently reported after dose 1 of the mRNA-1273 vaccine (2.6%). Differences by vaccine product following dose 1 were consistent by injection reaction type. Local reactions reported on day 14 after dose 1 were most common for females compared with males (2.0% vs. 0.4% overall; 3.6% vs. 0.7% for mRNA-1273; 0.3% vs. 0.1% for BNT162b2) and were generally similar across age groups (Fig. 2). Local reactions were less frequently reported on day 14 after dose 2 for both mRNA-1273 and BNT162b2 vaccines (0.2% and 0.2%, respectively). The proportion of participants reporting at least one solicited systemic reaction was similar by vaccine dose and product (2.3% mRNA-1273 dose 1, 1.9% mRNA-1273 dose 2, 2.0% BNT162b2 dose 1, 1.9% BNT162b2 dose 2). These systemic reactions were generally consistent across age groups and higher for females compared with males.

4. Discussion

From December 2020 through March 2021, over 4 million COVID-19 vaccine recipients provided information about their post-vaccination experience to the CDC v-safe surveillance system. During the first week following vaccination, we found that local and systemic reactions were common, and occurred more frequently after dose 2 and more frequently among mRNA-1273 recipients. Females and younger persons reported greater reactogenicity in the first week following first and second vaccine doses. In the second week post-vaccination, new or worsening injection site reactions were generally uncommon, and they were reported most frequently by females after dose 1 of the mRNA-1273 vaccine.

These findings concerning solicited local and systemic reactions in the first week following first and second doses of an mRNA-based COVID-19 vaccine are consistent with results reported from pre-authorization clinical trials [3,4]. For example, we found that at least two-thirds of participants reported injection site pain and about a third of participants reported fatigue and headache after dose 1; the proportions of participants reporting reactions were greater after dose 2, particularly for systemic reactions [3,4]. Similarly, a higher proportion of younger persons compared with older persons reported local or systemic reactions in v-safe and clinical trial data [3,4]. In v-safe, persons ≥65 years reported the least reactogenicity. This may be due in part to immunosenescence, or the waning immune response with advancing age [13,14], given some immunogenicity markers in early trial phases were lower in older adults [15,16]. Because reactogenicity is a product of early phases of the immune response to vaccines [13], it is possible that reduced immunogenicity could be related to age-specific patterns in reactogenicity. Yet, age-specific patterns in vaccine efficacy do not appear to be consistent with this hypothesis, given efficacy among those ≥65 years remained high in clinical trials (86% BNT162b2; 95% mRNA-1273) [3,4]. Older persons suffer the most morbidity and mortality associated with COVID-19 and would highly benefit from vaccination [17–19]. Other vaccines have demonstrated high series completion among older adults despite high reactogenicity if the perceived severity of the vaccine-preventable disease is also high [20]. It may be helpful for health care providers to mention this lower reactogenicity profile, assess perceptions of reactogenicity, and discuss the severity of COVID-19 with older persons who are particularly concerned about side effects from mRNA-based COVID-19 vaccines.

Reactogenicity results were not stratified by sex in clinical trials of mRNA COVID-19 vaccines [3,4]. In v-safe, we found that female participants reported greater reactogenicity after receiving mRNA vaccines and this finding was consistent by vaccine dose and product. Although sex differences may be due in part to differences in propensity to participate or report in v-safe, previous research on other vaccines has found that women more frequently report adverse reactions [21]. There may be biological mechanisms such as differences in genetic and hormonal factors that affect immune responses and thus the likelihood of greater reactogenicity [21]. These findings may help to inform female vaccine recipients about the potential for local or systemic reactions. They also might pro-

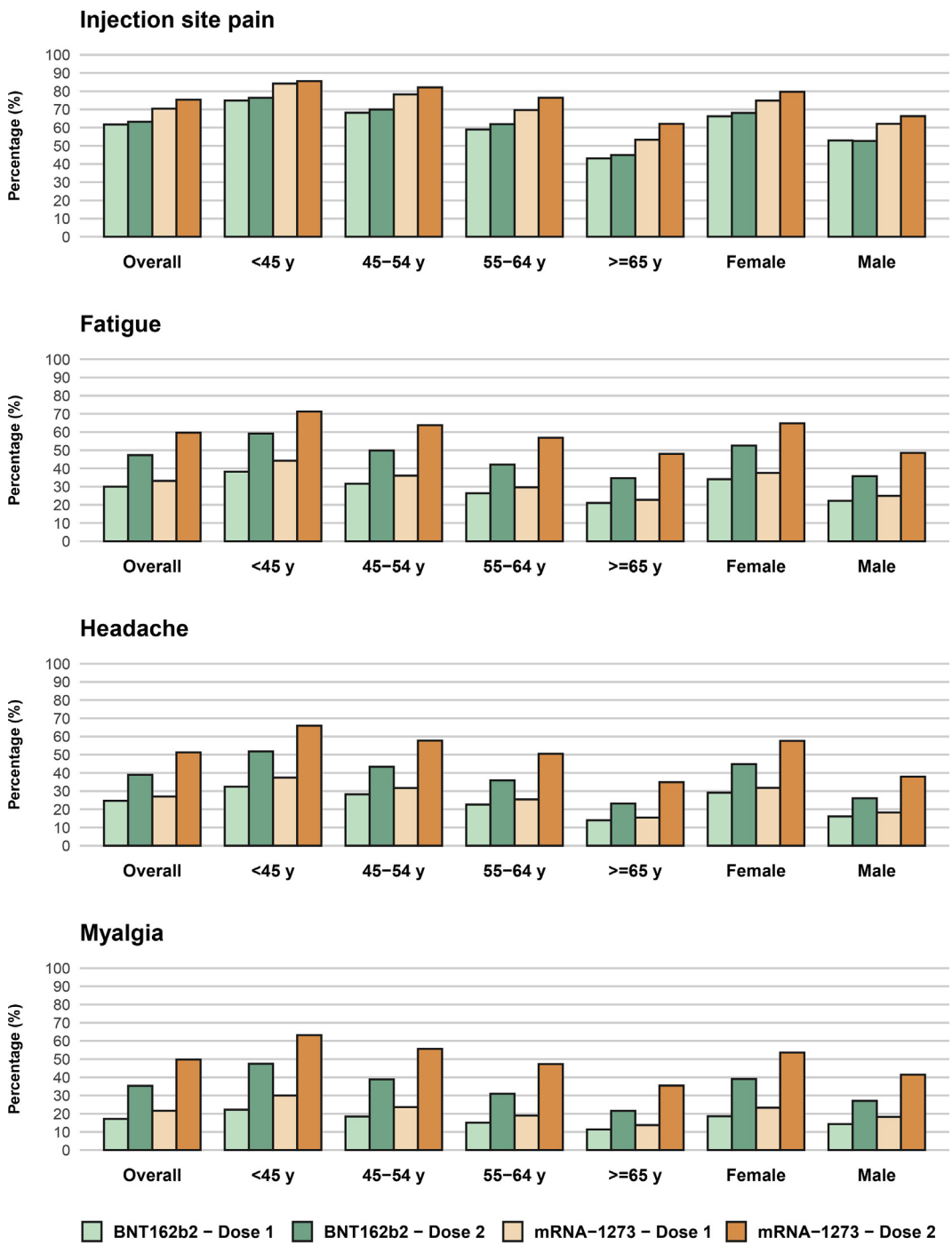

Fig. 1. Percentage of v-safe participants reporting local and systemic reactions to mRNA COVID-19 vaccines at least once during days 0–7 following vaccination by age and sex—CDC v-safe surveillance system, December 14, 2021 through March 28, 2021.

vide data for clinicians communicating with female patients about expectations of reactogenicity after mRNA-based COVID-19 vaccines.

While we confirmed that mRNA-based COVID-19 vaccines were associated with substantial levels of reactogenicity during the first week following administration, we found that new or worsening symptoms after the first week were uncommon. Less than 3 in 100 persons reported any of the assessed reactions on day 14 after either dose. Injection site reactions after dose 1 were the most salient reactions noted in the second week post-vaccination, followed by headache and fatigue. Although the BNT162b2 trial did not provide data about injection site reactions specifically after the first week, the mRNA-1273 trial did report that a small proportion of participants had injection site reactions on day 8 or later after vaccination (0.8%) [3,4]. Recent clinical reports have described such reactions in both BNT162b2 and mRNA-1273 recipients, and they may be more common in mRNA-1273 recipients [22,23]. Our results confirm that new or worsening injection site reactions may be reported during the second week after vaccination. In v-safe data, they were most frequently reported by mRNA-1273 recipients after dose 1. Yet, only 2.6% of participants reported injection site reactions during the second week after receiving mRNA-1273 dose 1 and even fewer reported reactions during the second week after dose 2. Because delayed injection site reactions may not

Table 3
Number and percentage of v-safe participants reporting new or worsening symptoms on day 14 following receipt of an mRNA COVID-19 vaccine—CDC v-safe surveillance system, December 14, 2021 through March 28, 2021.

	Both vaccines				BNT162b2				mRNA-1273			
	Dose 1 (N = 3,311,931)		Dose 2 (N = 2,252,809)		Dose 1 (N = 1,573,710)		Dose 2 (N = 1,061,536)		Dose 1 (N = 1,738,221)		Dose 2 (N = 1,191,273)	
	n	%	n	%	n	%	n	%	n	%	n	%
Any injection site reaction[1]	48,133	1.5	4,148	0.2	3,638	0.2	1,601	0.2	44,495	2.6	2,547	0.2
Injection site pain	12,705	0.4	2,778	0.1	2,164	0.1	1,219	0.1	10,541	0.6	1,559	0.1
Injection site redness	25,358	0.8	449	<0.1	860	0.1	121	<0.1	24,498	1.4	328	<0.1
Injection site swelling	15,915	0.5	520	<0.1	767	<0.1	198	<0.1	15,148	0.9	322	<0.1
Injection site itching	23,322	0.7	834	<0.1	950	0.1	193	<0.1	22,372	1.3	641	0.1
Injection site rash	15,182	0.5	653	<0.1	458	<0.1	173	<0.1	14,724	0.8	480	<0.1
COVID arm	2,007	0.1	50	<0.1	47	<0.1	<10	<0.1	1,960	0.1	44	<0.1
Any systemic reaction[2]	72,689	2.2	42,615	1.9	32,236	2.0	20,427	1.9	40,453	2.3	22,188	1.9
Fatigue	21,239	0.6	12,893	0.6	9,533	0.6	6,285	0.6	11,706	0.7	6,608	0.6
Headache	28,417	0.9	15,476	0.7	13,298	0.8	7,639	0.7	15,119	0.9	7,837	0.7
Myalgia	12,531	0.4	7,616	0.3	5,774	0.4	3,727	0.4	6,757	0.4	3,889	0.3
Chills	5,157	0.2	3,758	0.2	2,344	0.1	1,698	0.2	2,813	0.2	2,060	0.2
Fever	8,262	0.2	4,793	0.2	3,616	0.2	2,140	0.2	4,646	0.3	2,653	0.2
Joint Pain	4,699	0.1	3,403	0.2	2,074	0.1	1,617	0.2	2,625	0.2	1,786	0.1
Nausea	7,464	0.2	4,627	0.2	3,409	0.2	2,306	0.2	4,055	0.2	2,321	0.2
Vomiting	2,138	0.1	1,454	0.1	991	0.1	699	0.1	1,147	0.1	755	0.1
Diarrhea	6,938	0.2	4,170	0.2	3,272	0.2	2,029	0.2	3,666	0.2	2,141	0.2
Abdominal Pain	2,601	0.1	1,787	0.1	1,231	0.1	848	0.1	1,370	0.1	939	0.1
Rash outside of injection site	6,042	0.2	3,324	0.1	1,788	0.1	1,338	0.1	4,254	0.2	1,986	0.2

Abbreviations: COVID-19 = coronavirus disease 2019.
[1]**Any** of the listed injection site reactions.
[2]**Any** of the listed systemic reactions.

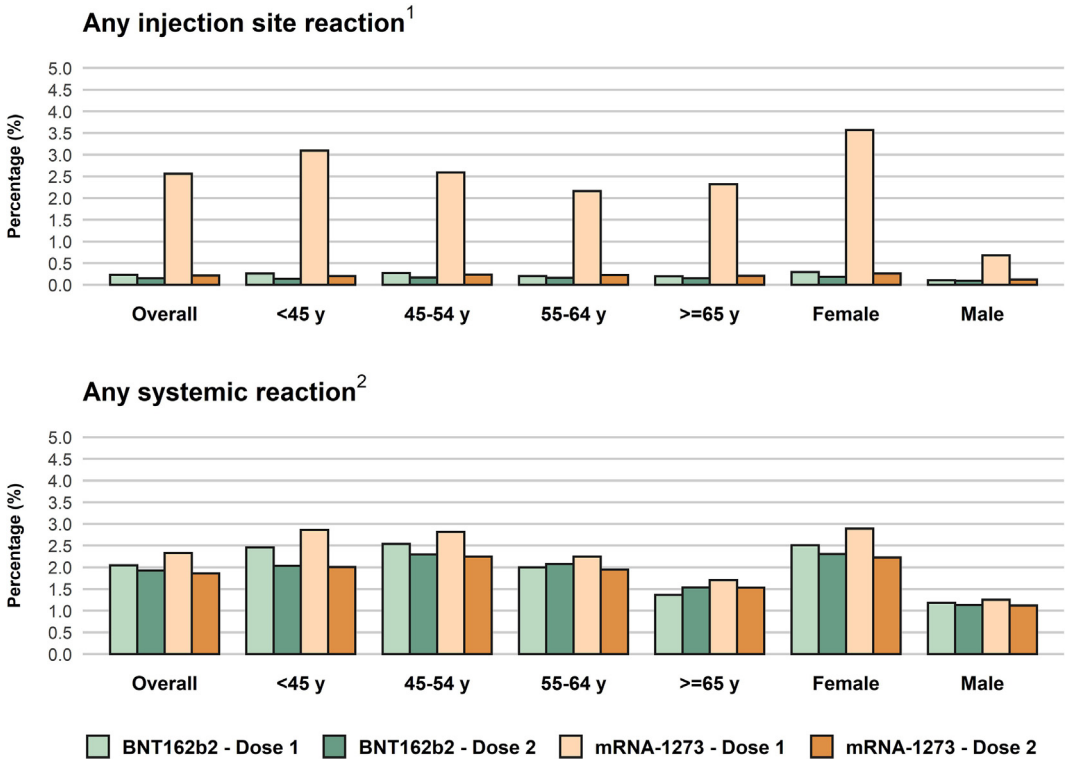

Fig. 2. Percentage of v-safe participants reporting new or worsening symptoms to mRNA COVID-19 vaccines on day 14[3] following vaccination by age and sex—CDC v-safe surveillance system, December 14, 2021 through March 28, 2021.
[1] Any injection reaction included any of the following: injection site pain, redness, swelling, itching, rash, or COVID arm.
[2] Any systemic reactions included any of the following: fatigue, headache, myalgia, chills, fever, joint pain, nausea, vomiting, diarrhea, abdominal pain, and rash outside of injection site.
[3] Reactions were quantified by applying text search methods to a free-text response on the day 14 survey that asked about new or worsening symptoms or health conditions since the participant's last survey.

be expected by vaccine recipients, it is important for healthcare providers to be aware that such reactions may develop in their patients. Patients may describe redness, swelling, itching, and rash near the injection site; these signs and symptoms might represent a delayed acute inflammatory response and differ from typical injection site reactions [10]. It is important to distinguish between

these delayed local hypersensitivity reactions and possible bacterial infections, as the former subsides without antibiotic treatment within days to weeks [10].

This study is subject to several limitations. First, the v-safe database includes less than 10% of vaccinated persons in the United States. By March 14, 2021, over 75 million U.S. residents had received one or more doses of an mRNA vaccine and 4,717,908 (6%) had enrolled in v-safe within a week after their first dose [24]. V-safe participants voluntarily self-enroll and promotion of v-safe enrollment may vary by type and location of a vaccination facility. Self-enrollment may allow for persons with post-vaccination reactogenicity to be more likely to enroll in v-safe, possibly overestimating the proportion reporting reactions. In addition, v-safe includes only COVID-19 vaccines and no unvaccinated control group was used for comparison to background rates of reactions. Further, this analysis covers a time period in which most U.S. citizens were eligible for COVID-19 vaccinees, but health care workers and essential workers received prioritization and had a longer eligibility period and therefore may be overrepresented in the v-safe population. Although use of a smartphone to complete surveys was not required, v-safe was developed so that smartphone users could easily register, receive text reminders, and complete web-based surveys. Therefore, the experiences reported by v-safe participants may not reflect those of the overall vaccinated U.S. population. For example, over the same time period, females represented about 59% of persons receiving at least one COVID-19 vaccine dose but accounted for 65% of dose 1 v-safe participants and persons ages ≥65 years represented about 48% of vaccinees but only 31% of dose 1 v-safe participants; thus v-safe participants may have had a greater representation of females and younger persons, both of whom we found to have greater reactogenicity in stratified analyses [25]. The day 14 free-text question was designed to collect information on new or worsening symptoms since the participant's last survey. For most participants the previous survey would have been completed on day 7 after vaccination; however, we did not examine whether differences in timing between surveys influenced responses. It is also possible that participants entered free-text information reflecting events outside of the second week following vaccination. Therefore, while we describe reactions reported on the day 14 survey, we cannot make conclusions about the date of onset or ensure that all reports were for new delayed-onset reactions. We used text search functions to classify free-text responses, and despite a refinement process, this system may be more prone to misclassification than validated coding systems (e.g., Medical Dictionary for Regulatory Activities (https://www.meddra.org/). For example, myalgia had lower sensitivity in our study, and although we refined associated terms, this could still result in underestimation of its prevalence. All v-safe measures are self-reported, therefore there may be some misclassification of outcomes, vaccine-related information, or demographics. Lastly, the local and systemic reactions described in this report did not include more rare and severe adverse reactions not intended for identification in v-safe data. A report using Vaccine Adverse Event Reporting System data has already estimated that rates of severe allergic reactions and anaphylaxis were 2.5 and 4.7 cases per million doses administered for the mRNA-1273 and BNT162b2 vaccines, respectively [26].

5. Conclusions

Despite the favorable safety profiles for mRNA-based COVID-19 vaccines established in clinical trials and early post-authorization monitoring, some persons may still harbor concerns about receiving these vaccines [3,4,6,7,26]. Though usually mild and transient [3,4,7], local and systemic reactions could have an important effect on each vaccine recipient's perceptions of the post-vaccination experience. Healthcare practitioners have an important role in discussing and addressing these patient concerns. Our findings from millions of v-safe responses suggest that common reactions following mRNA-based vaccines include injection site pain, fatigue, headache, myalgia, chills, fever, joint pain, injection site swelling, and nausea. These reactions are more common after the second dose. They are common for recipients of either of mRNA-based vaccine, although a higher proportion of mRNA-1273 recipients may experience these symptoms. These expected local and systemic reactions are part of the normal immunological response and typically resolve in a few days [3,4,7]. New or worsening injection site reactions in the second week after dose 1 are uncommon, but do occur, and clinicians should be aware that these can present as redness, swelling, itching, or rash near the injection site. These reactions differ from typical injection site reactions and likely represent a delayed acute inflammatory response that can resolve in days to weeks [10]. Offering this information to patients may help ease concerns about receiving a vaccine or completing a two-dose vaccine regimen [27]. Patient health materials that clearly communicate these expected, transient local and systemic reactions may help to engage in conversations about vaccination [28]. Providers can also use this information to prepare and set expectations with patients about their post-vaccination experience.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Mention of a product or company name is for identification purposes only and does not constitute endorsement by the CDC.

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.10.019.

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