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Safety of mRNA vaccines administered during the initial 6 months of the US COVID-19 vaccination programme: an observational study of reports to the Vaccine Adverse Event Reporting System and v-safe

Hannah G Rosenblum, Julianne Gee, Ruiling Liu, Paige L Marquez, Bicheng Zhang, Penelope Strid, Winston E Abara, Michael M McNeil, Tanya R Myers, Anne M Hause, John R Su, Lauri E Markowitz, Tom T Shimabukuro, David K Shay

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CDC COVID-19 Response Team (H G Rosenblum MD, J Gee MPH, R Liu PhD, P L Marquez MSPH, B Zhang MS, P Strid MPH, W E Abara MD, M M McNeil MD, T R Myers PhD, A M Hause PhD, J R Su MD, L E Markowitz MD, T T Shimabukuro MD, D K Shay MD) **and Epidemic Intelligence Service** (H G Rosenblum), **Centers for Disease Control and Prevention, Atlanta, GA, USA**

Correspondence to: Julianne Gee, CDC COVID-19 Response Team, Centers for Disease Control and Prevention, Atlanta, GA, USA **eocevent416@cdc.gov**

Summary

Background In December, 2020, two mRNA-based COVID-19 vaccines were authorised for use in the USA. We aimed to describe US surveillance data collected through the Vaccine Adverse Event Reporting System (VAERS), a passive system, and v-safe, a new active system, during the first 6 months of the US COVID-19 vaccination programme.

Methods In this observational study, we analysed data reported to VAERS and v-safe during Dec 14, 2020, to June 14, 2021. VAERS reports were categorised as non-serious, serious, or death. Reporting rates were calculated using numbers of COVID-19 doses administered as the denominator. We analysed v-safe survey reports from days 0–7 after vaccination for reactogenicity, severity (mild, moderate, or severe), and health impacts (ie, unable to perform normal daily activities, unable to work, or received care from a medical professional).

Findings During the study period, 298 792 852 doses of mRNA vaccines were administered in the USA. VAERS processed 340 522 reports: 313 499 (92·1%) were non-serious, 22 527 (6·6%) were serious (non-death), and 4496 (1·3%) were deaths. Over half of 7 914 583 v-safe participants self-reported local and systemic reactogenicity, more frequently after dose two (4 068 447 [71·7%] of 5 674 420 participants for local reactogenicity and 4 018 920 [70·8%] for systemic) than after dose one (4 644 989 [68·6%] of 6 775 515 participants for local reactogenicity and 3 573 429 [52·7%] for systemic). Injection-site pain (4 488 402 [66·2%] of 6 775 515 participants after dose one and 3 890 848 [68·6%] of 5 674 420 participants after dose two), fatigue (2 295 205 [33·9%] participants after dose one and 3 158 299 participants [55·7%] after dose two), and headache (1 831 471 [27·0%] participants after dose one and 2 623 721 [46·2%] participants after dose two) were commonly reported during days 0–7 following vaccination. Reactogenicity was reported most frequently the day after vaccination; most reactions were mild. More reports of being unable to work, do normal activities, or of seeking medical care occurred after dose two (1 821 421 [32·1%]) than after dose one (808 963 [11·9%]); less than 1% of participants reported seeking medical care after vaccination (56 647 [0·8%] after dose one and 53 077 [0·9%] after dose two).

Interpretation: Safety data from more than 298 million doses of mRNA COVID-19 vaccine administered in the first 6 months of the US vaccination programme show that most reported adverse events were mild and short in duration.

Funding US Centers for Disease Control and Prevention.

Introduction

In December, 2020, two mRNA COVID-19 vaccines (BNT162b2 [Pfizer-BioNTech]; and mRNA-1273 [Moderna]) were granted emergency use authorisation (EUA) by the US Food and Drug Administration (FDA) as two-dose series and recommended for use by the Advisory Committee on Immunization Practices (ACIP).[1,2] In clinical trials, both mRNA COVID-19 vaccines showed acceptable safety profiles;[3,4] the most frequently reported local and systemic symptoms were injection-site pain, fatigue, and headache. Reactogenicity was more frequently reported after dose two than after dose one and among participants younger than 65 years than among older participants.[3–5]

Post-authorisation safety monitoring can characterise the safety profiles of mRNA-based COVID-19 vaccines in large and heterogeneous populations.[6] Phased administration of COVID-19 vaccines in the USA began with health-care workers and long-term care-facility residents and was expanded to the general population during spring 2021; however, implementation plans varied by state.[7] The major sources of initial US safety data were the Vaccine Adverse Event Reporting System (VAERS), a spontaneous, passive reporting system;[8] and v-safe,[9] a new active monitoring system. VAERS was established in 1990 as the US early warning system to rapidly detect adverse events that might occur following vaccinations. V-safe was established in 2020 specifically for monitoring COVID-19 vaccine

Research in context

Evidence before this study

We searched PubMed for articles published up to Dec 29, 2021, using the terms ("BNT162b2" OR "mRNA-1273" OR "mRNA COVID-19 vaccine") AND ("reactogenicity" OR "side-effects" OR "adverse effects" OR "health impact"), not restricted by language or type of publication. Among 429 results, few publications described health impacts following vaccination by BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna). Available literature included reports of manufacturer-sponsored phase 1–3 clinical trials, observational and cross-sectional studies among specific groups (eg, transplant recipients or employees of a specific health-care system), and reviews or society recommendations that discussed reactogenicity and adverse events following mRNA vaccination.

Added value of this study

In this large, observational study, we assessed reactogenicity, health impacts, and adverse events reported following mRNA COVID-19 vaccination during the first 6 months of the US vaccination programme to one active (v-safe) and one passive (Vaccine Adverse Event Reporting System) surveillance system. We found that reported reactions to mRNA vaccination were mostly mild in severity and transient in duration, and most reports were non-serious. Reactions and health impacts were reported more frequently in female than in male recipients, and in individuals younger than 65 years than in older individuals. Information on health impacts for individuals from v-safe is presented here for the first time.

Implications of all the available evidence

The findings from two complementary surveillance systems from the first 6 months of mRNA vaccine administration in the USA are consistent with pre-authorisation clinical trials and early post-authorisation reports. On the basis of our findings, mild-to-moderate transient reactogenicity should be anticipated, particularly among younger and female vaccine recipients. Vaccine safety data collected by the US monitoring systems will be used to update the benefit–risk assessments for COVID-19 vaccine recommendations.

safety in the USA and collects information on reactogenicity and effects on health following COVID-19 vaccination.

Previous reports from these systems have been issued.[10–14] We aimed to review VAERS and v-safe data during the first 6 months of the US vaccination programme, when more than 298 million doses of mRNA COVID-19 vaccines were administered, to better characterise the safety profile of mRNA vaccines.

Methods

VAERS

VAERS is a national spontaneous reporting system for detecting potential adverse events for authorised or licensed US vaccines.[8] VAERS is co-administered by the US Centers for Disease Control and Prevention (CDC) and the US FDA. VAERS accepts reports from health-care providers and other members of the public primarily through online submissions and from vaccine manufacturers through electronic transmissions. The volume of mail, fax, and telephone reports is trivial compared with public online and manufacturer electronic submissions. Reports include information about the vaccinated person, type of vaccine administered, and adverse events experienced. A VAERS report can be submitted for any event experienced following receipt of a vaccine. We included all VAERS reports that were submitted for US residents who received mRNA vaccines and processed from Dec 14, 2020, to June 14, 2021, including any interval from vaccination to event report. Processed reports were quality checked, and submitted text on the adverse event was coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.[8] Each VAERS report was assigned at least one and possibly more than one MedDRA preferred term; preferred terms do not necessarily indicate medically confirmed diagnoses and they include signs and symptoms of illness and the ordering and results of diagnostic tests.

Based on the Code of Federal Regulations,[15] VAERS reports were classified as serious if any of the following outcomes were documented: inpatient hospitalisation, prolongation of hospitalisation, permanent disability, life-threatening illness, congenital anomaly or birth defect, or death. Prespecified adverse events of special interest were selected for enhanced monitoring of COVID-19 vaccine safety on the basis of biological plausibility, previous vaccine safety experience, and theoretical concerns related to COVID-19, such as vaccine-mediated enhanced disease.[16] VAERS staff requested death certificates and autopsy reports for reports of death. CDC physicians reviewed VAERS reports and available death certificates for each death to form an impression about cause of death. Impressions were assigned to one of the following categories: one of the 15 most common diagnostic categories from the International Classification of Disease, Tenth Revision, reported on US death certificates,[17] COVID-19 related, other (ie, impression was not included in prespecified categories), or unknown or unclear if not enough information were available to determine a cause of death.

V-safe

V-safe is a voluntary smartphone-based system that uses text messaging and secure web-based surveys to actively monitor COVID-19 vaccine safety for common local injection-site and systemic reactions.[9] V-safe participants receive text messages that link to web-based health check-in surveys following vaccination, initially daily

(days 0–7), then at longer intervals after vaccination. The system resets to the initial survey frequency after entry of another dose. We analysed survey reports from days 0–7 for reactogenicity, severity (mild, moderate, or severe),[9] and health impacts (ie, unable to perform normal daily activities, unable to work, or received care from a medical professional) that were submitted to v-safe between Dec 14, 2020, and June 14, 2021. Participants who reported receiving medical care were contacted and VAERS reports were completed, if clinically indicated.

For more on **federal regulations** see https://www.ecfr.gov/current/title-45

See Online for appendix

	Both mRNA vaccines (n=340 522)*	BNT162b2 vaccine (n=164 669)	mRNA-1273 vaccine (n=175 816)
Category			
Non-serious	313 499 (92·1%)	150 486 (91·4%)	162 977 (92·7%)
Serious, including death	27 023 (7·9%)	14 183 (8·6%)	12 839 (7·3%)
Serious, excluding death	22 527 (6·6%)	12 078 (7·3%)	10 448 (5·9%)
Death	4496 (1·3%)	2105 (1·3%)	2391 (1·4%)
Sex			
Female	246 085 (72·3%)	116 587 (70·8%)	129 475 (73·6%)
Male	88 311 (25·9%)	45 157 (27·4%)	43 140 (24·5%)
Unknown	6126 (1·8%)	2925 (1·8%)	3201 (1·8%)
Age, years			
16–17	6874 (2·0%)	3283 (2·0%)	3591 (2·0%)
18–49	154 171 (45·3%)	76 385 (46·4%)	77 773 (44·2%)
50–64	84 949 (24·9%)	40 367 (24·5%)	44 572 (25·4%)
65–74	49 755 (14·6%)	20 048 (12·2%)	29 702 (16·9%)
75–84	21 418 (6·3%)	9021 (5·5%)	12 392 (7·1%)
≥85	7595 (2·2%)	3564 (2·2%)	4027 (2·3%)
Unknown	15 760 (4·6%)	12 001 (7·3%)	3759 (2·1%)
Race or ethnicity†			
Hispanic or Latino	23 480 (6·9%)	11 217 (6·8%)	12 260 (7·0%)
Non-Hispanic			
White	169 877 (49·9%)	73 398 (44·6%)	96 469 (54·9%)
Black	10 446 (3·1%)	5104 (3·1%)	5342 (3·0%)
Asian	10 172 (3·0%)	5038 (3·1%)	5131 (2·9%)
American Indian or Alaska Native	1414 (0·4%)	615 (0·4%)	799 (0·5%)
Native Hawaiian or other Pacific Islander	441 (0·1%)	209 (0·1%)	232 (0·1%)
Multiple races	3542 (1·0%)	1578 (1·0%)	1964 (1·1%)
Other race	1684 (0·5%)	808 (0·5%)	876 (0·5%)
Unknown race	2593 (0·8%)	1422 (0·9%)	1171 (0·7%)
Unknown ethnicity			
White	28 787 (8·5%)	15 497 (9·4%)	13 289 (7·6%)
Black	4189 (1·2%)	2524 (1·5%)	1662 (1·0%)
Asian	2435 (0·7%)	1396 (0·9%)	1039 (0·6%)
American Indian or Alaska Native	724 (0·2%)	348 (0·2%)	375 (0·2%)
Native Hawaiian or other Pacific Islander	105 (<0·1%)	56 (<0·1%)	49 (<0·1%)
Multiple races	590 (0·2%)	301 (0·2%)	289 (0·2%)
Other race	4709 (1·4%)	2838 (1·7%)	1870 (1·1%)
Unknown race and ethnicity	75 334 (22·1%)	42 320 (25·7%)	32 999 (18·8%)

(Table 1 continues on next page)

Data analysis

We conducted descriptive analyses of available VAERS and v-safe data following dose one and dose two of BNT162b2 and mRNA-1273 vaccines among individuals aged at least 16 years. We stratified analyses by sex, age group, race and ethnicity, serious versus non-serious reports, and vaccine manufacturer; and for death reports, by time from vaccination to death (ie, onset interval) and cause of death. Reporting rates to VAERS were calculated for adverse events using the number of doses of mRNA vaccines administered during the 6-month period as the denominator. COVID-19 vaccine administration data were provided through CDC's COVID-19 Data Tracker.[18]

V-safe participants who responded to at least one health check-in survey during days 0–7 after vaccination were included in analyses. Descriptive statistics were calculated for participants' characteristics (sex, age, and race and ethnicity), reaction (type and severity) and health impact by manufacturer, dose number, and number of days following vaccination.

Analyses were done using SAS (version 9.4). Both VAERS and v-safe conduct surveillance as a public health function and are exempt from institutional review board review. Activities were reviewed by the CDC and done in accordance with applicable federal law and CDC policy.

Role of the funding source

Authors from the CDC, the funder, were responsible for study design, data analysis, data interpretation, and writing of the report.

Results

From Dec 14, 2020, to June 14, 2021, 298 792 852 doses of mRNA COVID-19 vaccines were administered in the USA: 167 177 332 were BNT162b2 and 131 639 515 were mRNA-1273 (appendix p 2). A greater proportion of vaccines was administered to females (155 969 573 [53·2%]) than to males (134 373 958 [45·8%]). The median age at vaccination was 50 years (IQR 33–65) for BNT162b2 and 56 years (39–68) for mRNA-1273. 112 698 875 (38·4%) recipients were non-Hispanic White. Race and ethnicity was unknown for 102 227 532 (34·9%) of all vaccine recipients.

During the study period, VAERS received and processed 340 522 reports: 164 669 following BNT162b2 and 175 816 following mRNA-1273 vaccination (table 1). Of these reports, 313 499 (92·1%) were classified as non-serious; 22 527 (6·6%) were serious, not resulting in death; and 4496 (1·3%) were deaths (table 1). 246 085 (72·3%) reports were among female participants and 154 171 (45·3%) reports were among those aged 18–49 years; median age was 50 years (IQR 36–64; table 1). 169 877 (49·9%) of those reporting race or ethnicity identified as non-Hispanic White, and for 75 334 (22·1%) race and ethnicity were

unknown (table 1). The most common MedDRA preferred terms assigned to non-serious reports were headache (64 064 [20·4%] of 313 499), fatigue (52 048 [16·6%]), pyrexia (51 023 [16·3%]), chills (49 234 [15·7%]), and pain (47 745 [15·2%]; table 1). The most common MedDRA preferred terms assigned to serious reports were dyspnoea (4175 [15·4%] of 27 023), death (3802 [14·1%]), pyrexia (2986 [11·0%]), fatigue (2608 [9·7%]), and headache (2567 [9·5%]; table 1).

The reporting rate to VAERS was 1049·2 non-serious reports per million vaccine doses, and 90·4 serious reports per million doses (table 2). Among the prespecified adverse events of special interest, reporting rates ranged from 0·1 narcolepsy reports per million doses administered to 31·3 reports of COVID-19 disease per million doses administered (table 2). 4496 reports of death were made to VAERS following receipt of an mRNA COVID-19 vaccine (table 3). After review by clinical staff, 25 reports were excluded because of miscoding of death or duplicate reporting. Of the 4471 reports of deaths analysed, 2086 (46·7%) were reported following BNT162b2 and 2385 (53·3%) following mRNA-1273. 1906 (42·6%) deaths were in female vaccine recipients and 2485 (55·6%) were in male recipients; the median age of participants who died was 76 years (IQR 66–86; table 3). 3647 (81·6%) deaths were reported among individuals aged 60 years or older (table 3). 821 (18·4%) deaths were identified as being in long-term care-facility residents. Time to death following vaccination was available for 4118 (92·1%) reports; median time was 10·0 days (IQR 3–25). The greatest number of death reports occurred on day 1 (470 [11·4%] of 4118) and day 2 (312 [7·6%] 4118) following vaccination (appendix p 10).

Death certificates or autopsy reports were available for clinical review for 808 (18·1%) of 4471 reports of deaths. Among these, causes of death were most commonly diseases of the heart (376 [46·5%]) and COVID-19 (102 [12·6%]; appendix pp 3–4). Among the 3663 reports of death without a death certificate or autopsy, causes of death were most commonly unknown or unclear (1984 [54·2%]), diseases of the heart (621 [17·0%]), and COVID-19 (317 [8·7%]; appendix pp 3–4). Causes of death among reports with death certificate or autopsy reports available are shown by age in appendix p 5.

During the study period, 7 914 583 mRNA COVID-19 vaccine recipients enrolled in v-safe after dose one or dose two and completed at least one post-vaccination health survey during days 0–7 (table 4). The median age of v-safe participants was 50 years (IQR 36–63), 4 975 209 (62·9%) were female, 2 860 738 (36·1%) were male, and 4 701 715 (59·4%) identified as non-Hispanic White (table 4). 6 775 515 participants completed at least one survey during days 0–7 after dose one (table 5). Of these participants, 4 644 989 (68·6%) reported a local injection-site reaction and 3 573 429 (52·7%) reported a systemic reaction (table 5). Of the 5 674 420 participants who completed surveys after dose two, 4 068 447 (71·7%) reported an injection-site reaction and 4 018 920 (70·8%) a systemic reaction (table 5). Local injection-site reactions were reported more frequently after mRNA-1273 than after BNT162b2 (table 5). A similar pattern was found for systemic reactions after mRNA-1273 versus BNT162b2 (table 5). The most frequently reported events after dose one of either mRNA vaccine included injection-site pain, fatigue, and headache, which were also more frequent after dose two than after dose one (table 5). Differences in proportions of reactogenicity by dose number were similar after stratifying by age (<65 *vs* ≥65 years) and sex (appendix p 6). More reactogenicity was reported among participants younger than 65 years than older participants and by female participants than male participants (appendix p 6).

Local and systemic reactions stratified by manufacturer, dose, days after vaccination, and severity are shown in the figure. Most reported symptoms were mild (figure). Participants reported moderate and severe reactogenicity most commonly on day 1 after dose two of either mRNA vaccine (figure). The proportion of

	Both mRNA vaccines (n=340 522)*	BNT162b2 vaccine (n=164 669)	mRNA-1273 vaccine (n=175 816)
(Continued from previous page)			
Signs or symptoms most frequently reported, non-serious‡			
Total	313 499	150 486	162 977
Headache	64 064 (20·4%)	30 907 (20·5%)	33 154 (20·3%)
Fatigue	52 048 (16·6%)	24 805 (16·5%)	27 241 (16·7%)
Pyrexia	51 023 (16·3%)	22 185 (14·7%)	28 837 (17·7%)
Chills	49 234 (15·7%)	21 638 (14·4%)	27 595 (16·9%)
Pain	47 745 (15·2%)	21 506 (14·3%)	26 238 (16·1%)
Nausea	37 333 (11·9%)	18 066 (12·0%)	19 267 (11·8%)
Dizziness	37 257 (11·9%)	20 307 (13·5%)	16 950 (10·4%)
Pain in extremity	31 753 (10·1%)	14 098 (9·4%)	17 653 (10·8%)
Injection-site pain	28 949 (9·2%)	10 462 (7·0%)	18 487 (11·3%)
Injection-site erythema	22 351 (7·1%)	2991 (2·0%)	19 360 (11·9%)
Signs or symptoms most frequently reported, serious‡			
Total	27 023	14 183	12 839
Dyspnoea	4175 (15·4%)	2210 (15·6%)	1965 (15·3%)
Death§	3802 (14·1%)	1753 (12·4%)	2039 (15·9%)
Pyrexia	2986 (11·0%)	1469 (10·4%)	1517 (11·8%)
Fatigue	2608 (9·7%)	1395 (9·8%)	1213 (9·4%)
Headache	2567 (9·5%)	1360 (9·6%)	1207 (9·4%)
Chest pain	2300 (8·5%)	1310 (9·2%)	990 (7·7%)
Nausea	2228 (8·2%)	1160 (8·2%)	1068 (8·3%)
Pain	2222 (8·2%)	1195 (8·4%)	1027 (8·0%)
Asthenia	2194 (8·1%)	1084 (7·6%)	1110 (8·6%)
Dizziness	2069 (7·7%)	1111 (7·8%)	958 (7·5%)

Data are n or n (%). Includes vaccines administered from Dec 14, 2020, to June 14, 2021. VAERS=Vaccine Adverse Event Reporting System. MedDRA=Medical Dictionary for Regulatory Activities. *Total includes reports without a vaccine manufacturer listed. †Race is not reported for individuals who identify as Hispanic or Latino, but it is reported for individuals with unknown ethnicity or non-Hispanic ethnicity. ‡Signs or symptoms refer to MedDRA preferred terms and are ordered by most frequently reported for both vaccines; MedDRA preferred terms are not mutually exclusive. §Not all reports of death were coded with the MedDRA preferred term of death.

Table 1: **Characteristics of reports received and processed by VAERS for mRNA COVID-19 vaccines**

	Both mRNA vaccines (n=298 792 852)		BNT162b2 vaccine (n=167 177 332)		mRNA-1273 vaccine (n=131 639 515)	
	n	Reports per million doses administered	n	Reports per million doses administered	n	Reports per million doses administered
Non-serious adverse event reports	313 499	1049·2	150 486	900·2	162 977	1238·1
Serious reports, including death	27 023	90·4	14 183	84·8	12 839	97·5
Serious reports, excluding death	22 527	75·4	12 078	72·2	10 448	79·4
Reports of adverse events of special interest*†						
COVID-19	9344	31·3	7184	43·0	2160	16·4
Coagulopathy‡	4320	14·5	2343	14·0	1977	15·0
Seizure	2733	9·1	1478	8·8	1255	9·5
Stroke§	1937	6·5	981	5·9	955	7·3
Bells' palsy	1918	6·4	1057	6·3	861	6·5
Anaphylaxis	1639	5·5	972	5·8	667	5·1
Myopericarditis	1307	4·4	813	4·9	494	3·8
Acute myocardial infarction	1118	3·7	610	3·6	508	3·9
Appendicitis	383	1·3	258	1·5	125	1·0
Guillain-Barré syndrome	293	1·0	154	0·9	139	1·1
Multisystem inflammatory syndrome in adults	119	0·4	60	0·4	59	0·4
Transverse myelitis	98	0·3	55	0·3	43	0·3
Narcolepsy	21	0·1	12	0·1	9	0·1

Includes vaccines administered from Dec 14, 2020, to June 14, 2021. VAERS=Vaccine Adverse Event Reporting System. *Represents reports, not confirmed by case definition. Events are not mutually exclusive. †Reported death is an adverse event of special interest but counts appear in tables 1 and 3. ‡Coagulopathy is an aggregate term capturing three specific adverse events: thrombocytopenia, deep venous thrombosis or pulmonary embolism, and disseminated intravascular coagulopathy. §No vaccine manufacturer was provided for one report of stroke.

Table 2: **Frequency and rates of adverse events of special interest reported to VAERS by recipients of mRNA COVID-19 vaccines**

	Both mRNA vaccines (n=4471*)		BNT162b2 vaccine (n=2086)		mRNA-1273 vaccine (n=2385)	
	n (%)	Reports per million doses administered†	n (%)	Reports per million doses administered†	n (%)	Reports per million doses administered†
Sex						
Female	1906 (42·6%)	12·2	918 (44·0%)	10·6	988 (41·4%)	14·2
Male	2485 (55·6%)	18·5	1116 (53·5%)	15·1	1369 (57·4%)	22·6
Unknown‡	80 (1·8%)	..	52 (2·5%)	..	28 (1·2%)	...
Age, years						
16–17	6 (0·1%)	1·1	6 (0·3%)	1·1	..	..
18–29	51 (1·1%)	1·3	27 (1·3%)	1·1	24 (1·0%)	1·6
30–39	94 (2·1%)	2·4	50 (2·4%)	2·2	44 (1·8%)	2·8
40–49	151 (3·4%)	3·8	74 (3·5%)	3·2	77 (3·2%)	4·6
50–59	328 (7·3%)	6·9	132 (6·3%)	5·0	196 (8·2%)	9·3
60–69	765 (17·1%)	14·4	354 (17·0%)	13·0	411 (17·2%)	16·0
70–79	1117 (25·0%)	28·5	496 (23·8%)	25·9	621 (26·0%)	31·0
80–89	1128 (25·2%)	75·4	529 (25·4%)	72·1	599 (25·1%)	78·6
≥90	637 (14·2%)	207·7	302 (14·5%)	188·1	335 (14·0%)	229·3
Unknown‡	194 (4·3%)	..	116 (5·6%)	..	78 (3·3%)	..

Includes reports made and vaccines administered from Dec 14, 2020, to June 14, 2021. VAERS=Vaccine Adverse Event Reporting System. *Of 4496 deaths, 25 were excluded as they could not be confirmed or were duplicate reports upon review. †Doses of vaccine administered in the study period were used for denominators in each age group; does not include doses administered in Texas because data for Texas were reported to the US Centers for Disease Control and Prevention in aggregate. ‡Reporting rates not shown for unknown categories because of unreliable dose denominators.

Table 3: **Frequency and rates of death reported to VAERS by recipients of mRNA COVID-19 vaccines, by sex and age group**

	Both mRNA vaccines (n=7 914 583)	BNT162b2 vaccine		mRNA-1273 vaccine	
		Dose one (n=3 455 778)	Dose two (n=2 920 526)	Dose one (n=3 319 737)	Dose two (n=2 753 894)
Sex					
Female	4 975 209 (62·9%)	2 150 068 (62·2%)	1 861 599 (63·7%)	2 073 542 (62·5%)	1 779 200 (64·6%)
Male	2 860 738 (36·1%)	1 272 011 (36·8%)	1 032 941 (35·4%)	1 210 622 (36·5%)	947 612 (34·4%)
Other	8872 (0·1%)	4027 (0·1%)	3464 (0·1%)	3443 (0·1%)	2947 (0·1%)
Prefer not to say	69 764 (0·9%)	29 672 (0·9%)	22 522 (0·8%)	32 130 (1·0%)	24 135 (0·9%)
Age, years					
16–17	73 347 (0·9%)	63 865 (1·8%)	38 530 (1·3%)	946 (0·03%)	473 (0·02%)
18–49	3 791 839 (47·9%)	1 726 465 (50·0%)	1 431 627 (49·0%)	1 505 760 (45·4%)	1 219 210 (44·3%)
50–59	1 500 981 (19·0%)	653 799 (18·9%)	574 422 (19·7%)	627 214 (18·9%)	531 200 (19·3%)
60–64	739 381 (9·3%)	315 404 (9·1%)	279 350 (9·6%)	316 768 (9·5%)	270 831 (9·8%)
65–74	1 344 721 (17·0%)	516 227 (14·9%)	452 928 (15·5%)	643 663 (19·4%)	557 279 (20·2%)
≥75	464 314 (5·9%)	180 018 (5·2%)	143 669 (4·9%)	225 386 (6·8%)	174 901 (6·4%)
Race or ethnicity*					
Hispanic	782 301 (9·9%)	346 197 (10·0%)	288 263 (9·9%)	316 460 (9·5%)	256 185 (9·3%)
Non-Hispanic					
White	4 701 715 (59·4%)	2 059 560 (59·6%)	1 896 823 (64·9%)	1 979 056 (59·6%)	1 830 413 (66·5%)
Black	443 938 (5·6%)	202 598 (5·9%)	176 164 (6·0%)	178 981 (5·4%)	153 667 (5·6%)
Asian	467 932 (5·9%)	215 713 (6·2%)	196 173 (6·7%)	154 498 (4·7%)	138 793 (5·0%)
American Indian or Alaska Native	27 899 (0·4%)	11 161 (0·3%)	9194 (0·3%)	13 486 (0·4%)	11 410 (0·4%)
Native Hawaiian or other Pacific Islander	19 393 (0·2%)	8500 (0·2%)	7373 (0·3%)	7689 (0·2%)	6664 (0·2%)
Multiple races	110 326 (1·4%)	50 954 (1·5%)	46 129 (1·6%)	41 977 (1·3%)	38 772 (1·4%)
Other race	42 230 (0·5%)	19 252 (0·6%)	16 757 (0·6%)	15 885 (0·5%)	13 880 (0·5%)
Unknown race	23 420 (0·3%)	10 249 (0·3%)	9090 (0·3%)	9502 (0·3%)	8270 (0·3%)
Unknown ethnicity†					
White	115 766 (1·5%)	48 084 (1·4%)	38 674 (1·3%)	52 143 (1·6%)	42 070 (1·5%)
Black	26 865 (0·3%)	11 602 (0·3%)	8570 (0·3%)	11 993 (0·4%)	8406 (0·3%)
Asian	33 146 (0·4%)	14 134 (0·4%)	11 844 (0·4%)	11 356 (0·3%)	9153 (0·3%)
American Indian or Alaska Native	3142 (<0·1%)	1206 (<0·1%)	848 (<0·1%)	1582 (<0·1%)	1151 (<0·1%)
Native Hawaiian or other Pacific Islander	1945 (<0·1%)	815 (<0·1%)	659 (<0·1%)	800 (<0·1%)	613 (<0·1%)
Multiple races	6,370 (0·1%)	2902 (0·1%)	2408 (0·1%)	2478 (0·1%)	2041 (0·1%)
Other race	13 148 (0·2%)	5681 (0·2%)	4528 (0·2%)	5414 (0·2%)	4263 (0·2%)
Unknown race and ethnicity†	129 647 (1·6%)	56 481 (1·6%)	45 410 (1·6%)	54 969 (1·7%)	44 340 (1·6%)
Unavailable‡	965 400 (12·2%)	390 689 (11·3%)	161 619 (5·5%)	461 468 (13·9%)	183 803 (6·7%)
Pregnant at time of vaccination	86 801 (1·1%)	39 884 (1·2%)	39 163 (1·3%)	25 255 (0·8%)	25 428 (0·9%)
Pregnancy test positive after vaccination	27 370 (0·3%)	1548 (<0·1%)	11 677 (0·4%)	4009 (0·1%)	10 199 (0·4%)

Data are n (%). Includes vaccines administered from Dec 14, 2020, to June 14, 2021. *Race is not reported for individuals who identify as Hispanic or Latino, but it is reported for individuals with unknown ethnicity or non-Hispanic ethnicity. †Unknown indicates that v-safe participants selected unknown or preferred not to say. ‡Unavailable refers to information that was not collected or was missing in v-safe.

Table 4: **Demographic characteristics of v-safe participants reporting receipt of an mRNA COVID-19 vaccine and completing at least one health survey 0–7 days after vaccination**

participants who reported symptoms was greatest on day 1 and then decreased subsequently (figure). The highest proportions of participants reporting severe symptoms occurred on day 1 following dose two of mRNA-1273 (appendix p 8). On all other days, proportions of participants reporting severe symptoms did not exceed 3·0% for any individual symptom (appendix pp 7–8).

Reported health impacts were greater following dose two of either vaccine than dose one, and after mRNA-1273

	Both mRNA vaccines		BNT162b2 vaccine		mRNA-1273 vaccine	
	Dose one (n=6 775 515)	Dose two (n=5 674 420)	Dose one (n=3 455 778)	Dose two (n=2 920 526)	Dose one (n=3 319 737)	Dose two (n=2 753 894)
Any injection-site reaction*	4 644 989 (68·6%)	4 068 447 (71·7%)	2 212 051 (64·0%)	1 908 124 (65·3%)	2 432 938 (73·3%)	2 160 323 (78·4%)
Injection-site pain	4 488 402 (66·2%)	3 890 848 (68·6%)	2 140 843 (61·9%)	1 835 398 (62·8%)	2 347 559 (70·7%)	2 055 450 (74·6%)
Swelling	703 790 (10·4%)	976 946 (17·2%)	246 230 (7·1%)	309 718 (10·6%)	457 560 (13·8%)	667 228 (24·2%)
Redness	353 788 (5·2%)	640 739 (11·3%)	116 108 (3·4%)	167 127 (5·7%)	237 680 (7·2%)	473 612 (17·2%)
Itching	376 076 (5·6%)	605 633 (10·7%)	145 596 (4·2%)	191 132 (6·5%)	230 480 (6·9%)	414 501 (15·1%)
Any systemic reaction*	3 573 429 (52·7%)	4 018 920 (70·8%)	1 771 509 (51·3%)	1 931 643 (66·1%)	1 801 920 (54·3%)	2 087 277 (75·8%)
Fatigue	2 295 205 (33·9%)	3 158 299 (55·7%)	1 127 904 (32·6%)	1 475 646 (50·5%)	1 167 301 (35·2%)	1 682 653 (61·1%)
Headache	1 831 471 (27·0%)	2 623 721 (46·2%)	893 992 (25·9%)	1 189 444 (40·7%)	937 479 (28·2%)	1 434 277 (52·1%)
Myalgia	1 423 336 (21·0%)	2 478 170 (43·7%)	653 821 (18·9%)	1 085 365 (37·2%)	769 515 (23·2%)	1 392 805 (50·6%)
Chills	631 546 (9·3%)	1 680 185 (29·6%)	263 617 (7·6%)	642 856 (22·0%)	367 929 (11·1%)	1 037 329 (37·7%)
Fever	642 092 (9·5%)	1 679 577 (29·6%)	274 650 (7·9%)	656 454 (22·5%)	367 442 (11·1%)	1 023 123 (37·2%)
Joint pain	642 006 (9·5%)	1 440 927 (25·4%)	285 812 (8·3%)	591 877 (20·3%)	356 194 (10·7%)	849 050 (30·8%)
Nausea	562 273 (8·3%)	901 103 (15·9%)	267 160 (7·7%)	384 525 (13·2%)	295 113 (8·9%)	516 578 (18·8%)
Diarrhoea	383 576 (5·7%)	419 044 (7·4%)	190 542 (5·5%)	198 618 (6·8%)	193 034 (5·8%)	220 426 (8·0%)
Abdominal pain	233 511 (3·4%)	359 107 (6·3%)	113 872 (3·3%)	158 251 (5·4%)	119 639 (3·6%)	200 856 (7·3%)
Rash	85 766 (1·3%)	99 878 (1·8%)	41 565 (1·2%)	42 662 (1·5%)	44 201 (1·3%)	57 216 (2·1%)
Vomiting	55 710 (0·8%)	91 727 (1·6%)	25 336 (0·7%)	36 761 (1·3%)	30 374 (0·9%)	54 966 (2·0%)
With reported health impacts*	808 963 (11·9%)	1 821 421 (32·1%)	361 834 (10·5%)	740 529 (25·4%)	447 129 (13·5%)	1 080 892 (39·2%)
Unable to do normal activity	658 330 (9·7%)	1 501 679 (26·5%)	290 207 (8·4%)	598 584 (20·5%)	368 123 (11·1%)	903 095 (32·8%)
Unable to work	305 709 (4·5%)	911 366 (16·1%)	135 063 (3·9%)	360 411 (12·3%)	170 646 (5·1%)	550 955 (20·0%)
Reported medical care	56 647 (0·8%)	53 077 (0·9%)	27 358 (0·8%)	25 568 (0·9%)	29 289 (0·9%)	27 509 (1·0%)
Telehealth consultation	19 562 (0·3%)	19 770 (0·3%)	9318 (0·3%)	9238 (0·3%)	10 244 (0·3%)	10 532 (0·4%)
Clinic attendance	18 671 (0·3%)	16 793 (0·3%)	9109 (0·3%)	8487 (0·3%)	9562 (0·3%)	8306 (0·3%)
Emergency room visit	9907 (0·1%)	8907 (0·2%)	5087 (0·1%)	4494 (0·2%)	4820 (0·1%)	4413 (0·2%)
Hospitalisation	1896 (<0·1%)	2053 (<0·1%)	915 (<0·1%)	1001 (<0·1%)	981 (<0·1%)	1052 (<0·1%)

Data are n (%). Includes health check-in surveys made and vaccines administered from Dec 14, 2020, to June 14, 2021. *Reports of local and systemic reactions and reported health impacts are not mutually exclusive.

Table 5: **Local and systemic reactions and health impacts following mRNA COVID-19 vaccines reported during days 0–7 after vaccination to v-safe, by manufacturer and dose**

than after BNT162b2 (table 5). After dose two of BNT162b2, 598 584 (20·5%) of 2 920 526 participants were unable to do normal activities, and 360 411 (12·3%) were unable to work (table 5). After dose two of mRNA-1273, 903 095 (32·8%) of 2 753 894 participants were unable to do normal activities, and 550 955 (20·0%) were unable to work (table 5). Less than 1·0% reported receiving medical care after receiving either dose of either vaccine (table 5). A very small proportion reported an emergency room visit or hospitalisation (table 5).

When stratified by sex, female participants reported a health impact more frequently than did male participants, peaking on day 1 after vaccination (appendix p 11). Following dose two of mRNA-1273 vaccine, 522 192 (41·4%) of 1 262 711 female participants reported an inability to do normal activities in the day 1 survey, and 296 178 (23·5%) reported an inability to work (appendix pp 9, 11). Among male recipients of dose two of mRNA-1273, on the day 1 survey 167 957 (25·6%) of 655 688 were unable to do normal activity and 110 868 (16·9%) were unable to work (appendix pp 9, 11).

Discussion

In this analysis of VAERS and v-safe data from the first 6 months of COVID-19 vaccination rollout in the USA, when over 298 million doses of mRNA vaccines were administered, we found that reactogenicity was similar to what was reported from clinical trials and from early post-authorisation monitoring.[3–5,10,11] In both VAERS and v-safe, local injection-site and systemic reactions were commonly reported. V-safe participants more frequently reported transient reactions following mRNA-1273 than following BNT162b2, and more frequently following dose two of either vaccine compared with after dose one. Female participants and individuals younger than 65 years reported adverse events and reactions more frequently than male participants and those aged 65 years and older, respectively. Reporting rates for death were higher in

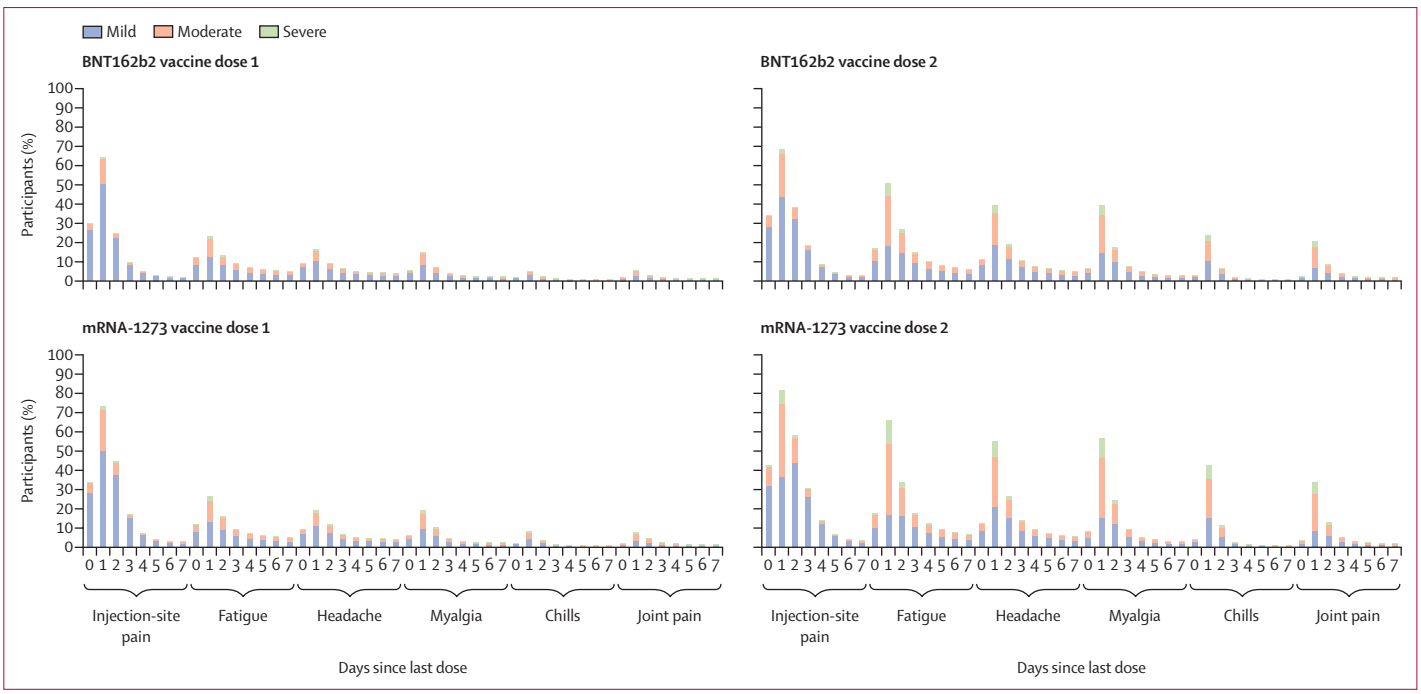

***Figure*: Local and systemic reactions to mRNA COVID-19 vaccines reported to v-safe, by manufacturer, dose, days after vaccination, and severity**
Figure shows top reactions by reported frequency, after showing by dose number and by manufacturer. These top six reactions were determined by reported frequency after dose two of both mRNA COVID-19 vaccines in v-safe, excluding fever because it was not rated mild, moderate, or severe. Mild was defined as "noticeable symptoms but they aren't a problem", moderate as "symptoms that limit normal activities", and severe as "make normal daily activities difficult or impossible".

older age groups, as expected on the basis of general age-specific mortality in the general adult population.

Safety monitoring of COVID-19 vaccines has been the most comprehensive in US history and has used established systems, including the Vaccine Safety Datalink (VSD),[19] VAERS, and a new system, v-safe, developed specifically for monitoring COVID-19 vaccine safety. During the study period, all COVID-19 vaccines were administered under EUAs, which require vaccine providers to report all serious adverse events (including deaths) that occur after vaccination to VAERS, regardless of whether they were plausibly associated with vaccination. Heightened public awareness of the COVID-19 vaccination programme, outreach and education to health-care providers and hospitals about COVID-19 EUA reporting requirements for adverse events, and adherence to EUA reporting requirements by providers and health systems, probably all contributed to the high volume of VAERS reports received.

Data from US safety monitoring systems for all COVID-19 vaccines authorised or approved by the FDA have been reviewed regularly by the ACIP COVID-19 Vaccines Safety Technical Work Group[20] and at public ACIP meetings.[21] Similar to reports following receipt of other vaccines routinely administered to adults, most VAERS reports following mRNA COVID-19 vaccination were non-serious.[22–25] Serious adverse events detected in VAERS and VSD[26] surveillance prompted specific safety evaluations for anaphylaxis,[14] thrombosis with thrombocytopenia syndrome,[27] myocarditis,[28] and Guillain-Barré syndrome.[29] After reports of anaphylaxis following mRNA vaccination with both vaccines, clinical guidance and management recommendations were updated.[30] Also during this time period, a safety signal for myocarditis was identified and investigated further in VAERS and other US safety systems.[31,32] Thrombosis with thrombocytopenia syndrome[27] and Guillain-Barré syndrome[29] have been associated with Janssen's Ad26.COV2.S adenoviral vector COVID-19 vaccine but not with mRNA vaccines. ACIP has conducted several benefit–risk assessments for each of the authorised or approved US COVID-19 vaccines;[21,27–29] these assessments have resulted in several modifications to clinical guidance and a preferential recommendation for mRNA vaccines.[30]

Reactogenicity findings following mRNA COVID-19 vaccination from VAERS and v-safe data are similar to those from a large study in the UK.[33] The observed patterns might be explained in part by host characteristics known to influence reactogenicity, including age, sex, and the presence of underlying medical conditions.[34] Female recipients have more vigorous antibody responses[35] to certain vaccines and also tend to report more severe local and systemic reactions to influenza vaccine, compared with male recipients.[36] Female recipients might also be more likely than male recipients to respond to surveys.[37,38] Younger people might be more comfortable with smartphone-based surveys and more likely to respond to surveys generally.[39,40]

Using v-safe data, we were able to assess the effects of mRNA vaccination on daily-life activities among vaccine recipients for the first time for a vaccine administered in the USA. These effects were most frequently reported on day 1 after vaccination. Reports about the measures of health impacts used in v-safe, although self-assessed and subjective, correlate with reports about reactogenicity: more health impacts were reported by female than by male recipients, by participants younger than 65 years compared with older participants, after dose two compared with dose one, and by those who received mRNA-1273 versus BNT162b2. Reports of seeking medical care after mRNA vaccine were rare; v-safe surveys did not ask which symptoms prompted the participant to seek medical care. Reactogenicity and its associated health impacts, even if transient, might deter some from seeking vaccination. Surveys found that nearly half of unvaccinated adults younger than 50 years expressed concern about missing work because of vaccine side-effects and that employees who were given paid leave were more likely to get vaccinated than were those without paid leave;[41] employer policies that accommodate such leave might increase vaccination coverage.[42]

In our review and analysis of death reports to VAERS following mRNA vaccination, we found no unusual patterns in cause of death among the death reports received. Under the COVID-19 vaccine EUA regulations, health-care providers are required to report deaths and life-threatening adverse health events after COVID-19 vaccinations to VAERS regardless of their potential association with vaccination. These requirements make comparing the number of reported deaths to VAERS for COVID-19 vaccines with reported deaths following other adult vaccines[43] difficult because no other adult vaccines have been so widely administered under FDA EUAs. Initially, US COVID-19 vaccination was prioritised for individuals aged 65 years and older and those in long-term care facilities.[7] These populations have the highest baseline mortality risk, complicating comparisons with mortality reporting for other adult vaccines. Similar to general mortality in the adult population,[44] reporting rates for deaths in this analysis increased with increasing age. The concentrated reporting of deaths on the first few days after vaccination follows patterns similar to those observed for other adult vaccinations.[45] This pattern might represent reporting bias because the likelihood to report a serious adverse event might increase when it occurs in close temporal proximity to vaccination.

There are limitations in any review of preliminary data concerning reports of death following vaccination. A comparison with national mortality data[44] suggests that certain causes of death, such as accidents, suicides, or cancer, are less likely to be reported to VAERS. Underreporting to VAERS, in general, is expected.[8] The predominance of heart disease as a cause of death reported to VAERS warrants continued monitoring and assessment but might be driven by non-specific causes, such as cardiac arrest, that might be chosen as a terminal event if no immediate explanation for death was available. Death certificate or autopsy reports were available for only a small proportion of deaths reported to VAERS when our analyses were conducted. Finally, VAERS is designed as an early warning system to detect potential safety signals,[8] and VAERS data alone generally cannot establish causal relationships between vaccination and adverse events. Another surveillance system, the VSD, showed no increased risk of non-COVID-19 mortality in vaccinated people.[46]

This study has several strengths, including the large population under surveillance and the comprehensive capture of national data from two complementary surveillance systems. Because the US Government purchased all COVID-19 doses and collected administration data, we were able to calculate VAERS reporting rates using the number of mRNA vaccine doses administered as denominators.[18] By contrast, VAERS analyses for non-COVID-19 vaccines rely on doses distributed, not administered. Because the number of doses distributed is greater than that of doses administered, these past VAERS analyses are likely to underestimate reporting rates of vaccine-related adverse events. Information from v-safe about how reactogenicity during the week after mRNA vaccination affects daily activities and work is novel and provides new insights.

An important limitation of this report is one shared by all VAERS analyses: we used data from a passive reporting system subject to underreporting and variable or incomplete reporting.[8] Although VAERS death reports were individually reviewed by CDC physicians and follow-up is ongoing to obtain additional and missing records, other reports of serious adverse events were not individually reviewed. Additionally, VAERS reports require interpretation to identify whether reports meet clinical case definitions.[47] A limitation of v-safe is the need for smartphone access. Because a subset of all vaccine recipients participated in v-safe, the results are unlikely to be generalisable to the entire vaccinated US population. Other differences might exist among participants who received mRNA-1273 or BNT162b2 vaccines that were unaccounted for; therefore, v-safe cannot be used to draw conclusions that one mRNA vaccine type is more reactogenic than the other. Additionally, participants in v-safe might be lost to follow-up because continuous enrolment is not required. Finally, this report only included v-safe responses received during the first week after vaccination.

During the first 6 months of the US COVID-19 vaccination programme, more than 50% of the eligible population received at least one vaccine dose. VAERS and v-safe data from this period show a post-authorisation safety profile for mRNA COVID-19 vaccines that is generally consistent with pre-authorisation trials[3,4]

and early post-authorisation surveillance reports.[10,11] Serious adverse events, including myocarditis, have been identified following mRNA vaccinations; however, these events are rare. Vaccines are the most effective tool to prevent serious COVID-19 disease outcomes[48] and the benefits of immunisation in preventing serious morbidity and mortality strongly favour vaccination.[27–29] VAERS and v-safe, two complementary surveillance systems, will continue to provide data needed to inform policy makers, immunisation providers, other health-care professionals, and the public about the safety of COVID-19 vaccination.

Contributors

HGR, JG, JRS, TRM, AMH, LEM, TTS, and DKS contributed to conceptualisation, data curation, formal analysis, investigation, methodology, project administration, visualisation, writing, and editing. JRS, TRM, TTS, DKS, JG, and LEM contributed to supervision. RL, PLM, and BZ contributed to data curation, formal analysis, validation, visualisation, writing, and editing, and have verified the underlying data. WEA and MMM contributed to data curation, analysis, writing, and editing. PS contributed to project administration, visualisation, writing, and editing. All authors had access to the underlying data of the study and were responsible for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

US COVID-19 vaccine administration data are available at https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total. VAERS data, redacted of personal identifying information and other sensitive information, can be accessed at https://vaers.hhs.gov/data.html. Per-protocol (https://www.cdc.gov/vaccinesafety/pdf/V-safe-Protocol-508.pdf), final de-identified v-safe data will be made available at the end of the v-safe programme. Protocols and standard operating procedures for COVID-19 for both systems are available at https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/emergencypreparedness/index.html.

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