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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

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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, 298792852 doses of mRNA vaccines were administered in the USA. VAERS processed 340522 reports: 313499 (92.1%) were non-serious, 22527 (6.6%) were serious (non-death), and 4496 (1.3%) were deaths. Over half of 7914583 v-safe participants self-reported local and systemic reactogenicity, more frequently after dose two (4068447 [71.7%] of 5674420 participants for local reactogenicity and 4018920 [70.8%] for systemic) than after dose one (4644989 [68.6%] of 6775515 participants for local reactogenicity and 3573429 [52.7%] for systemic). Injection-site pain (4488402 [66.2%] of 6775515 participants after dose one and 3890848 [68.6%] of 5674420 participants after dose two), fatigue (2295205 [33.9%] participants after dose one and 3158299 participants [55.7%] after dose two), and headache (1831471 [27.0%] participants after dose one and 2623721 [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 (1821421 [32.1%]) than after dose one (808963 [11.9%]); less than 1% of participants reported seeking medical care after vaccination (56647 [0.8%] after dose one and 53077 [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.

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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). In clinical trials, both mRNA COVID-19 vaccines showed acceptable safety profiles, 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. Post-authorisation safety monitoring can characterise the safety profiles of mRNA-based COVID-19 vaccines in large and heterogeneous populations. 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. The major sources of initial US safety data were the Vaccine Adverse Event Reporting System (VAERS), a spontaneous, passive reporting system; and v-safe, 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
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.\textsuperscript{8–14} 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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{6} 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.\textsuperscript{6} 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,\textsuperscript{7} 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.\textsuperscript{7} 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), 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.

**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. 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, 298792852 doses of mRNA COVID-19 vaccines were administered in the USA: 167177332 were BNT162b2 and 131639515 were mRNA-1273 (appendix p 2). A greater proportion of vaccines was administered to females (155969753 [53.2%]) than to males (134373958 [45.8%]). The median age at vaccination was 50 years (IQR 33–65) for BNT162b2 and 56 years (39–68) for mRNA-1273. 112698875 (38.4%) recipients were non-Hispanic White. Race and ethnicity was unknown for 102227532 (34.9%) of all vaccine recipients.

During the study period, VAERS received and processed 340522 reports: 164669 following BNT162b2 and 175816 following mRNA-1273 vaccination (table I). Of these reports, 313499 (92.1%) were classified as non-serious; 22527 (6.6%) were serious, not resulting in death; and 4496 (1.3%) were deaths (table I). 246085 (72.3%) reports were among female participants and 154171 (45.3%) reports were among those aged 18–49 years; median age was 50 years (IQR 36–64; table I). 169877 (49.9%) of those reporting race or ethnicity identified as non-Hispanic White, and for 75334 (22.1%) race and ethnicity were

### Table 1

| Category | Both mRNA vaccines (n=340522) | BNT162b2 vaccine (n=164669) | mRNA-1273 vaccine (n=175816) |
|----------|------------------------------|-----------------------------|------------------------------|
| Non-serious | 313499 (92.1%) | 150486 (91.4%) | 162977 (92.7%) |
| Serious, including death | 27023 (7.9%) | 14183 (8.6%) | 12839 (7.3%) |
| Serious, excluding death | 22527 (6.6%) | 12076 (7.3%) | 10448 (5.9%) |
| Death | 4496 (1.3%) | 2103 (1.3%) | 2391 (1.4%) |
| Sex | | | |
| Female | 246685 (72.3%) | 116587 (70.8%) | 129475 (73.6%) |
| Male | 88321 (25.9%) | 45157 (27.4%) | 43140 (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 | 154171 (45.3%) | 76385 (46.4%) | 77773 (44.2%) |
| 50–64 | 84949 (24.9%) | 40367 (24.5%) | 44572 (25.4%) |
| 65–74 | 49755 (14.6%) | 20048 (12.2%) | 29702 (16.9%) |
| 75–84 | 21418 (6.3%) | 9021 (5.5%) | 12392 (7.1%) |
| ≥85 | 7595 (2.2%) | 3564 (2.2%) | 4072 (2.3%) |
| Unknown | 15760 (4.6%) | 12001 (7.3%) | 3759 (2.1%) |
| Race or ethnicity | | | |
| Hispanic or Latino | 23480 (6.9%) | 11217 (6.8%) | 12266 (7.0%) |
| Non-Hispanic | | | |
| White | 169877 (49.9%) | 73398 (44.6%) | 96469 (54.9%) |
| Black | 10446 (3.1%) | 5104 (3.1%) | 5342 (3.0%) |
| Asian | 10172 (2.9%) | 5038 (3.1%) | 5133 (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%) | 1121 (0.7%) |
| Unknown ethnicity | | | |
| White | 28787 (8.5%) | 15497 (9.4%) | 13289 (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 | 75334 (22.1%) | 42320 (25.7%) | 32999 (18.8%) |

(Table 1 continues on next page)
unknown (table 1). The most common MedDRA preferred terms assigned to non-serious reports were headache (64064 [20.4%] of 313499), fatigue (52048 [16.6%]), pyrexia (51023 [16.3%]), chills (49234 [15.7%]), and pain (47745 [15.2%]; table 1). The most common MedDRA preferred terms assigned to serious reports were dyspnoea (4175 [15.4%] of 27023), 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). 821 (18.4%) deaths occurred on day 1 (470 [11.1%] of 4118) following vaccination (appendix p 10).

Death certificates or autopsy reports were available for 4418 (92.1%) reports; median time was 10.0 days (IQR 3–25). The greatest number of death reports occurred on day 1 (470 [11.1%] 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, 7914583 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), 4973209 (62.9%) were female, 2860738 (36.1%) were male, and 4701715 (59.4%) identified as non-Hispanic White (table 4). 6775515 participants completed at least one survey during days 0–7 after dose one (table 5). Of these participants, 4644989 (68.6%) reported a local injection-site reaction and 3573429 (52.7%) reported a systemic reaction (table 5). Of the 5674420 participants who completed surveys after dose two, 4068447 (71.7%) reported an injection-site reaction and 401920 (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

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

|                        | Both mRNA vaccines (n=340522)* | BNT162b2 vaccine (n=164669) | mRNA-1273 vaccine (n=175816) |
|------------------------|-------------------------------|-------------------------------|-------------------------------|
| **Total**              | 331349                        | 150486                        | 162977                        |
| **Deaths**             |                                | 17532                         | 12824                         |
| 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%)                   | 1355 (9.8%)                   | 1213 (9.4%)                   |
| Headache               | 2567 (9.5%)                   | 1306 (9.6%)                   | 1207 (9.4%)                   |
| Chest pain             | 2300 (8.5%)                   | 1310 (9.2%)                   | 990 (7.7%)                    |
| Asthenia               | 2228 (8.2%)                   | 1160 (8.2%)                   | 1068 (8.3%)                   |
| Pain                   | 2222 (8.2%)                   | 1195 (8.4%)                   | 1027 (8.0%)                   |
| Anorexia               | 2104 (8.1%)                   | 1084 (7.6%)                   | 1110 (8.6%)                   |
| Dizziness              | 2059 (7.7%)                   | 1111 (7.8%)                   | 958 (7.5%)                    |

Data are n or n (%). Includes vaccines administered from Dec 14, 2020, to June 30, 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.
Both mRNA vaccines (n=298 792 852)  BNT162b2 vaccine (n=167 177 332)  mRNA-1273 vaccine (n=131 639 515)

|                        | Both mRNA vaccines | BNT162b2 vaccine | mRNA-1273 vaccine |
|------------------------|--------------------|-------------------|-------------------|
| n                      | 313 499            | 150 486           | 162 977           |
| Reports per million    | 1049 2             | 900 2             | 1238 1            |
| doses administered     |                    |                   |                   |
| Non-serious adverse event reports | 27 023             | 14 183            | 12 839            |
| Serious reports, including death | 22 527             | 12 078            | 10 448            |
| Serious reports, excluding death |                  |                   |                   |

| Reports of adverse events of special interest*† | Both mRNA vaccines | BNT162b2 vaccine | mRNA-1273 vaccine |
|-----------------------------------------------|--------------------|-------------------|-------------------|
| COVId-19                                      | 9344               | 7184              | 2160              |
| Coagulopathy†                                  | 4320               | 2343              | 1977              |
| Seizure                                       | 2733               | 1478              | 1255              |
| Stroke                                        | 1937               | 981               | 955               |
| Bell’s palsy                                   | 1918               | 1057              | 861               |
| Anaphylaxis                                    | 1639               | 922               | 667               |
| Myopericarditis                                | 1207               | 813               | 494               |
| Acute myocardial infarction                   | 1118               | 610               | 508               |
| Appendicitis                                  | 383                | 258               | 125               |
| Guillain-Barré syndrome                        | 293                | 154               | 139               |
| Multisystem inflammatory syndrome in adults   | 119                | 60                | 59                |
| Transverse myelitis                            | 98                 | 55                | 43                |
| Narcolepsy                                    | 21                 | 12                | 9                 |

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)

|                        | Both mRNA vaccines | BNT162b2 vaccine | mRNA-1273 vaccine |
|------------------------|--------------------|-------------------|-------------------|
| n (%)                  | 1906 (42.6%)       | 918 (44.0%)       | 988 (41.4%)       |
| Reports per million    | 12.2               | 10.6              | 14.2              |
| doses administered     |                    |                   |                   |
| unknown‡               | 80 (1.8%)          | 52 (2.5%)         | 28 (1.2%)         |

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 | BNT162b2 vaccine | mRNA-1273 vaccine |
|------------------------|--------------------|-------------------|-------------------|
| n (%)                  | 1906 (42.6%)       | 918 (44.0%)       | 988 (41.4%)       |
| Reports per million    | 12.2               | 10.6              | 14.2              |
| doses administered     |                    |                   |                   |
| unknown‡               | 80 (1.8%)          | 52 (2.5%)         | 28 (1.2%)         |

Includes reports made and 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.
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

| Race or ethnicity* | Both mRNA vaccines (n=7914583) | BNT162b2 vaccine | mRNA-1273 vaccine |
|-------------------|--------------------------------|------------------|-----------------|
|                   | Dose one (n=3455778) | Dose two (n=2920526) | Dose one (n=3319737) | Dose two (n=2753894) |
| Male              | 2860738 (36.1%) | 1272011 (36.8%) | 1032494 (35.4%) | 1210622 (36.5%) |
| Female            | 4975209 (62.9%) | 2150668 (62.2%) | 1861999 (62.7%) | 2073542 (62.5%) |
| Prefer not to say | 69764 (0.9%) | 29672 (0.9%) | 22522 (0.8%) | 32130 (1.0%) |
| Age, years        |                    |                  |                  |                  |
| 16–17             | 73347 (0.9%) | 63865 (1.8%) | 38530 (1.3%) | 946 (0.03%) |
| 18–49             | 3791839 (47.9%) | 1728465 (50.0%) | 1431627 (49.0%) | 1505760 (45.4%) |
| 50–59             | 1500981 (19.0%) | 651799 (18.9%) | 574422 (19.7%) | 627214 (18.9%) |
| 60–64             | 739381 (9.3%) | 315404 (9.1%) | 279350 (9.6%) | 316768 (9.5%) |
| 65–74             | 1344721 (17.0%) | 516277 (14.9%) | 452928 (15.5%) | 643663 (19.4%) |
| ≥75               | 464314 (5.9%) | 180018 (5.2%) | 143669 (4.9%) | 225386 (6.8%) |
| Race or ethnicity† |                    |                  |                  |                  |
| Hispanic          | 782301 (9.9%) | 346197 (10.0%) | 288263 (9.9%) | 316460 (9.5%) |
| Non-Hispanic      |                    |                  |                  | 256185 (9.3%) |
| White             | 4701715 (59.4%) | 2095960 (59.9%) | 1896852 (64.9%) | 1979056 (59.6%) |
| Black             | 443938 (5.6%) | 202598 (5.9%) | 176164 (6.0%) | 178981 (5.4%) |
| Asian             | 467932 (5.9%) | 255733 (7.2%) | 195173 (6.7%) | 154498 (4.7%) |
| American Indian or Alaska Native | 27899 (0.4%) | 11161 (0.3%) | 9194 (0.3%) | 13486 (0.4%) |
| Native Hawaiian or other Pacific Islander | 19393 (0.2%) | 8500 (0.2%) | 7373 (0.3%) | 7689 (0.2%) |
| Multiple races    | 110226 (1.4%) | 50954 (1.5%) | 46129 (1.6%) | 41977 (1.3%) |
| Other race        | 42230 (0.5%) | 19252 (0.6%) | 16757 (0.6%) | 15885 (0.5%) |
| Unknown race      | 42420 (0.3%) | 10249 (0.3%) | 9090 (0.3%) | 9502 (0.3%) |
| Unknown ethnicity‡ |                    |                  |                  |                  |
| White             | 115766 (1.5%) | 48804 (1.4%) | 38674 (1.3%) | 52143 (1.6%) |
| Black             | 26865 (0.3%) | 11602 (0.3%) | 8570 (0.3%) | 11993 (0.4%) |
| Asian             | 33146 (0.4%) | 14134 (0.4%) | 11844 (0.4%) | 11356 (0.3%) |
| American Indian or Alaska Native | 3142 (0.1%) | 1206 (0.1%) | 848 (<0.1%) | 1582 (<0.1%) |
| Native Hawaiian or other Pacific Islander | 1945 (0.1%) | 815 (<0.1%) | 659 (<0.1%) | 800 (<0.1%) |
| Multiple races    | 6370 (0.1%) | 2902 (0.1%) | 2408 (0.1%) | 2478 (0.1%) |
| Other race        | 13148 (0.2%) | 5681 (0.2%) | 4528 (0.2%) | 5414 (0.2%) |
| Unknown race and ethnicity§ | 129647 (1.6%) | 56481 (1.6%) | 45410 (1.6%) | 54969 (1.7%) |
| Unavailable†      | 965400 (12.2%) | 390889 (11.3%) | 161619 (5.5%) | 461468 (33.9%) |
| Pregnant at time of vaccination | 86801 (1.1%) | 39884 (1.2%) | 31163 (1.3%) | 25255 (0.8%) |
| Pregnancy test positive after vaccination | 27370 (0.3%) | 1548 (<0.1%) | 11677 (0.4%) | 4099 (0.1%) |

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
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. 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

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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
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), 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 and at public ACIP meetings. Similar to reports following receipt of other vaccines routinely administered to adults, most VAERS reports following mRNA COVID-19 vaccination were non-serious. Serious adverse events detected in VAERS and VSD surveillance prompted specific safety evaluations for anaphylaxis, thrombocytopenia syndrome, myocarditis, and Guillain-Barré syndrome. After reports of anaphylaxis following mRNA vaccination with both vaccines, clinical guidance and management recommendations were updated. Also during this time period, a safety signal for myocarditis was identified and investigated further in VAERS and other US safety systems. Thrombosis with thrombocytopenia syndrome and Guillain-Barré syndrome 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; these assessments have resulted in several modifications to clinical guidance and a preferential recommendation for mRNA vaccines.

Reactogenicity findings following mRNA COVID-19 vaccination from VAERS and v-safe data are similar to those from a large study in the UK. 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. Female recipients have more vigorous antibody responses to certain vaccines and also tend to report more severe local and systemic reactions to influenza vaccine, compared with male recipients. Female recipients might also be more likely than male recipients to respond to surveys. Younger people might be more comfortable with smartphone-based surveys and more likely to respond to surveys generally.

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”.

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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 determine 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 vaccines43 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,64 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.65 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 data66 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.7 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.9 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.6 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.67 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 enrollment 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 trials68.
and early post-authorisation safety reports.\textsuperscript{11,13} 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\textsuperscript{48} and the benefits of immunisation in preventing serious morbidity and mortality strongly favour vaccination.\textsuperscript{22–29} 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/ensuring-safety/monitoring/emergency-use-preparedness/index.html.

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