Severe systemic adverse events following mRNA COVID-19 vaccination among those with prior history of SARS-CoV-2 infection – v-safe nested case-control study

Version 1
May 27, 2021

Project summary

The primary goal of this project is to assess the association between history of SARS-CoV-2 infection prior to vaccination and severe systemic adverse events (i.e., those resulting in medical attention by an emergency department or hospitalization) within 7 days following receipt of the first dose of an mRNA COVID-19 vaccine. Two mRNA COVID-19 vaccines have been granted Emergency Use Authorization by the U.S. Food and Drug Administration (BNT162b2 mRNA vaccine manufactured by Pfizer-BioNTech and mRNA-1273 vaccine manufactured by Moderna). There is evidence that incidence of certain systemic adverse reactions following receipt of the first mRNA vaccine dose may be greater among those with a prior history of a COVID-19 diagnosis compared with immunologically naïve persons. Because persons with a clear history of a previous COVID-19 diagnosis were excluded from participating in the mRNA COVID-19 vaccine clinical trials, our understanding of adverse events following COVID-19 vaccination among those with a prior history of COVID-19 is incomplete.

The U.S. Centers for Disease Control and Prevention (CDC) may be able to assess how a history of SARS-CoV-2 infection may affect reactogenicity following vaccination through its vaccine safety monitoring system. V-safe is an active smartphone-based system that uses text messaging to initiate web-based surveys to monitor for adverse events following COVID-19 vaccination. It sends health surveys daily on days 0–7 and weekly starting on day 14 (week 2) up to day 42 (week 6), following each vaccine dose, and then at 3, 6, and 12 months post-vaccination. V-safe registrants report vaccine info, symptoms and their severity, and the health impact of symptoms reported. We plan to conduct a nested case-control study within v-safe.

Cases and controls will be identified using v-safe survey responses. Case-patients will be defined as v-safe registrants who reported systemic symptoms or health conditions resulting in medical attention including an emergency department visit or hospitalization on days 0–7 following the first dose of COVID-19 mRNA vaccine. Controls will be v-safe registrants who (1) were the same age (in years) as their corresponding case-patient when they received the first vaccine dose (registrants ≥ 90 years were treated as the same age), (2) were vaccinated within 3 days of their corresponding case-patient's vaccination date, (3) completed a health check-in survey on the survey day their corresponding case-patient reported an emergency department visit or hospitalization due to a systemic adverse event, (4) were non-cases on the day that their corresponding case-patient reported an emergency department visit or hospitalization, (5) had no prior reports of seeking medical attention, including care via telehealth, outpatient/urgent care center, emergency department, or hospitalization, following the first dose of COVID-19 mRNA vaccine. A ratio of three controls per case is desired.

V-safe does not collect information on SARS-CoV-2 infection prior to vaccination; thus, diagnosis information will need to be collected from case-patients and controls via a separate follow-up survey. Case-patients and controls will be contacted by text message using the telephone numbers they provided when they enrolled in v-safe. If the registrant agrees to participate, they will be directed to the survey and will respond to the follow-up questions using their smartphone. Follow-up survey questions include participant history of SARS-CoV-2 infection prior to COVID-19 vaccination, verification of case/control status, demographics, history of anaphylaxis following past vaccination, and underlying medical conditions.

The primary analysis will assess the association between history of SARS-CoV-2 infection (defined as infection detected by a nucleic acid amplification test) preceding vaccination and severe systemic adverse events during the 7 days following receipt of the first dose of an mRNA COVID-19 vaccine. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for severe adverse events will be calculated using conditional logistic regression, controlling for sex, race/ethnicity, vaccine manufacturer, and history of anaphylaxis following vaccination.

Background and significance

In December 2020, the U.S. Food and Drug Administration (FDA) granted Emergency Use Authorization to two mRNA vaccines (BNT162b2 mRNA vaccine manufactured by Pfizer-BioNTech; mRNA-1273 vaccine manufactured by Moderna) for the prevention of coronavirus disease 2019 (COVID-19), the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1, 2] Preliminary data from each candidate's Phase 3 trial showed substantial local and systemic reactogenicity following both vaccine doses.[3, 4] For example, after the first dose of the Moderna vaccine, 87.8% of participants reported any adverse reaction, 84.2% reported any local adverse reaction, and 54.9% reported any systemic adverse reaction.[4] Following the second dose, the percentage of participants reporting any, local, and systemic adverse reactions increased to 92.2%, 88.6%, and 79.4%, respectively.[4]

Persons with a known history of a previous COVID-19 diagnosis were excluded from participating in these two COVID-19 vaccine clinical trials. Thus, our understanding of adverse events following COVID-19 vaccination among those with a history of COVID-19 remains incomplete. However, because results of baseline SARS-CoV-2 tests were not immediately

available, some clinical trial participants whose baseline SARS-CoV-2 test results were positive received the first dose of vaccine; information on this population of participants was reported.[4] During the Phase 3 trial of mRNA-1273, 679 participants were considered SARS-CoV-2 positive at baseline, by seroconversion to the SARS-CoV-2 nucleocapsid protein or by a positive reverse transcription polymerase chain reaction [RT-PCR] test.[4] Of these, 337 were in the placebo group and 342 were in the mRNA-1273 group. There was evidence that incidence of certain systemic adverse reactions may have been greater among those considered baseline SARS-CoV-2 positive compared to those considered baseline SARS-CoV-2 negative (61.4% vs. 54.7%, respectively) following the first dose of vaccine. An inverse relationship between baseline SARS-CoV-2 status and adverse reactions was observed for local adverse reactions following dose 1 of vaccine and all adverse reactions following dose 2 of vaccine. These participants, however, reflect a small sample and may not be representative of the population of individuals with prior SARS-CoV-2 infection, especially those with symptomatic infection, as participants who tested positive at baseline during clinical trials were asymptomatic.

A study involving healthcare workers reported similar findings following dose 1 of mRNA COVID-19 vaccine.[5] Healthcare workers with SARS-CoV-2 antibodies prior to vaccination experienced systemic adverse events at higher frequencies than seronegative individuals after the first dose. Information regarding adverse event severity was limited in this report, and severity of prior SARS-CoV-2 infection was not reported.

CDC may be able to assess how a history of SARS-CoV-2 infection prior to vaccination may affect reactogenicity following vaccination through its vaccine safety monitoring system. This

system includes the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), the Clinical Immunization Safety Assessment (CISA) Project, and a project started to provide more active safety surveillance for the COVID-19 immunization program, v-safe. V-safe was determined to be the best suited of these systems for assessing relationships between a history of SARS-CoV-2 infection prior to vaccination and adverse events following vaccination.

V-safe is an active smartphone-based system that uses text messaging to initiate web-based surveys to monitor for adverse events following COVID-19 vaccination. It sends reminders to participants for health surveys on days 0–7, and weekly starting on day 14 (week 2) up to day 42 (week 6), following each vaccine dose, and then at 3, 6, and 12 months post-vaccination. Registrants report vaccine info, symptoms and their severity, and the health impact of symptoms reported. V-safe does not collect information on SARS-CoV-2 infection prior to vaccination (however, it is requested in weekly and monthly surveys post-vaccination); thus, this information on retrospective SARS-CoV-2 infections before vaccination will need to be collected separately via follow-up with a subset of registrants.

Goals and objectives

The goal of this project is to assess the association between SARS-CoV-2 infection prior to COVID-19 vaccination and systemic adverse events resulting in medical attention by an emergency department or hospitalization following receipt of the first dose of an mRNA COVID-19 vaccine. This project is being conducted solely for the purpose of providing timely

information to inform and update clinical recommendations for vaccine administration in the context of the COVID-19 pandemic.

Objective

- To determine if vaccinated persons with grade 4 systemic adverse events (i.e., systemic adverse events resulting in an emergency department visit or hospitalization) following receipt of the first dose of an mRNA COVID-19 vaccine are more likely to have received a positive SARS-CoV-2 test prior to vaccination compared with vaccinated persons with non-severe (i.e., not requiring medical attention) or no systemic reactions.

Potential subanalyses

- Moderna versus Pfizer vaccine
- History of SARS-CoV-2 infection prior to vaccination and differences in adverse events following first dose versus second dose
- Differences in the type, frequency, and duration of adverse events reported
- History of symptomatic versus asymptomatic SARS-CoV-2 infection or no history of SARS-CoV-2 infection
- Severity of SARS-CoV-2 infection (medical attention required and level of medical attention)
- History of SARS-CoV-2 infection (using confirmatory, presumptive, or supportive laboratory evidence) versus no history of SARS-CoV-2 infection
- Time elapsed between SARS-CoV-2 infection and vaccination
- Age or other demographic differences

Methods

Project design

We will use a nested case-control design for this project. Cases and controls will be selected from the v-safe health check-in database. We will restrict to v-safe registrants who reported receiving a Pfizer or Moderna COVID-19 mRNA vaccine and were aged 18 years and older at the time of the first vaccine dose. We will exclude registrants who reported pregnancy and those with modified survey data or indeterminable survey response days. We will consider vaccination dates from December 14, 2020 through 7 days before the initiation of case selection.

Case-patients will be defined as v-safe registrants who reported systemic symptoms or health conditions resulting in medical attention including an emergency department visit or hospitalization on days 0–7 following the first dose of COVID-19 mRNA vaccine.

Controls will be v-safe registrants who (1) were the same age (in years) as their corresponding case-patient when they received the first vaccine dose (those ≥ 90 years were treated as the same age), (2) were vaccinated within 3 days of their corresponding case-patient's vaccination date, (3) completed a health check-in survey on the survey day their corresponding case-patient reported an emergency department visit or hospitalization due to a systemic adverse event, (4) were non-cases on the day that their corresponding case-patient reported an emergency department visit or hospitalization, (5) had no prior reports of seeking medical attention, including care via telehealth, outpatient/urgent care center, emergency department, or hospitalization, following the first dose of COVID-19 mRNA vaccine. It is possible that an

individual selected as a control may go on to become a case-patient, and that an individual may be selected as a control for multiple case-patients.

Controls will be oversampled using a multiplier of four. If control participation for a given case exceeds the target, we will randomly select which controls will be included in our analysis.

Case-patients and controls will be contacted using the telephone numbers registrants provided when they enrolled in v-safe. Text messages will be used to invite selected v-safe registrants to participate in this project, and a link to the survey will be provided in the message. Case-patients and controls will receive up to two text messages (the initial message and one reminder message, if needed). Text messages will be sent at 10:00 a.m. according to the registrant's time zone. The selected registrant may also receive a phone call reminder if needed. If we still do not receive a response through the text message survey after these contact attempts, the selected registrant will be replaced.

If the registrant agrees to participate in this project, they will be directed to the survey and will respond to the questions using their smartphone. Survey questions include participant history of SARS-CoV-2 infection, verification of case/control status, demographics (including race, ethnicity, occupation, residence in a long-term care facility), history of anaphylaxis following past vaccination, and underlying medical conditions. (See Attachment 1 for questionnaire items.) Surveys will be available in five languages: English, Spanish, Simplified Chinese, Korean, and Vietnamese (consistent with languages offered in v-safe). It will take an estimated 5 minutes for participants to respond to all questions.

If a participant reports a history of a positive SARS-CoV-2 test, the survey team may contact them by phone call for additional information to verify their test result. The survey team may ask participants who self-reported positive viral SARS-CoV-2 test results if they would be willing to share test result reports. If a participant agrees, they will be provided with the email address for a mailbox managed by the survey team and asked to email their result report. Participants will be provided with a unique identification number to include with their test result report and asked to remove all personally identifiable information from the report. Test result reports will be deleted after the test results are verified.

Case, control, and exposure definitions

Cases. Case-patients will be defined as v-safe registrants who reported systemic symptoms or health conditions resulting in medical attention including an emergency department visit or hospitalization on days 0–7 following the first dose of COVID-19 mRNA vaccine.

Controls. Controls will be v-safe registrants who (1) were the same age (in years) as their corresponding case-patient when they received the first vaccine dose (those ≥ 90 years were treated as the same age), (2) were vaccinated within 3 days of their corresponding case-patient's vaccination date, (3) completed a health check-in survey on the survey day their corresponding case-patient reported an emergency department visit or hospitalization due to a systemic adverse event, (4) were non-cases on the day that their corresponding case-patient reported an emergency department visit or hospitalization, (5) had no prior reports of seeking medical attention, including care via telehealth, outpatient/urgent care center, emergency department, or

hospitalization, following the first dose of COVID-19 mRNA vaccine. It is possible that a control may go on to become a case-patient, and that an individual may be selected as a control for multiple case-patients.

A ratio of three controls per case is desired. However, if we are unable to obtain a sufficient number of controls to maintain this ratio, we will adjust our target control to case ratio (see Table 1 for sample size calculations).

Exposure. The exposure of interest is a history of SARS-CoV-2 infection preceding vaccination. Participants will be asked to self-report their test results, test type, and approximate test date. If a participant reports a history of a positive viral SARS-CoV-2 test, the survey team may contact them by phone call for additional information to verify their test result.

The primary analysis will use confirmatory laboratory evidence of SARS-CoV-2 infection, defined as infection with SARS-CoV-2 detected by a nucleic acid amplification test.

Subanalyses may also consider combinations of confirmatory laboratory evidence (via nucleic acid amplification test), presumptive laboratory evidence (via antigen test), and supportive laboratory evidence (via antibody test) of SARS-CoV-2 infection versus no laboratory evidence of SARS-CoV-2 infection.

Sample size calculations

Table 1 shows the sample size needed for this project assuming a significance level (α) of 0.05, power (1-β) of 0.80, and 4.5% prevalence of history of COVID-19 among controls, by different control:case ratios.

Table 1. Expected number of cases needed to detect a given odds ratio, by ratio of controls:cases (α = 0.05, β = 0.2, prevalence of history of COVID-19 among controls = 4.5%)

-	**Number of Cases (Total Sample Size)**		
Controls:Cases	**OR = 1.25**	**OR = 1.50**	**OR = 1.75**
1:1	7336 (14,672)	2222 (4,444)	1167 (2,334)
2:1	5502 (16,506)	1667 (5,001)	875 (2,625)
3:1	4891 (19,564)	1482 (5,928)	778 (3,112)

Survey variables

Variables that will be extracted from the v-safe database include registrant's age at vaccination, sex, vaccination date, dose number, vaccine manufacturer, symptoms reported during health check-ins, symptom severity, health impact of symptoms reported, including where medical care was received (if applicable), and pregnancy.

Variables that will be collected from participants using the questionnaire delivered through text message include history of a positive SARS-CoV-2 test result, date of positive SARS-CoV-2 test, type of SARS-CoV-2 test, COVID-19 symptoms and severity, race, ethnicity, occupation,

residence in a long-term care facility, history of anaphylaxis following vaccination, and chronic underlying medical conditions. We will also verify case and control status. (See Attachment 1 for questionnaire items.)

Data analysis plan

Descriptive analyses stratified by case status will be conducted. Variables considered include age, sex, race/ethnicity, occupation, residence in a long-term care facility, history of anaphylaxis following vaccination, chronic underlying medical conditions, vaccine manufacturer, history of a positive SARS-CoV-2 test, months elapsed between positive SARS-CoV-2 test and first COVID-19 vaccine dose (if applicable), symptomatic COVID-19 (if applicable), and COVID-19 severity (if applicable; defined as illness that resulted in medical attention). (See Table 1 in Attachment 2 for table shell.)

Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for severe adverse events (i.e., systemic adverse events resulting in an emergency department visit or hospitalization) will be calculated using conditional logistic regression. The primary analysis will assess the relationship between history of SARS-CoV-2 infection detected using a confirmatory test (i.e., a nucleic acid amplification test) preceding vaccination and severe systemic adverse events during the 7 days following receipt of the first dose of an mRNA COVID-19 vaccine. Adjusted results will control for sex, race/ethnicity, vaccine manufacturer, and history of anaphylaxis following vaccination. (See Table 2 in Attachment 2 for table shell.) Data will be analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

Other COVID-19 vaccine products authorized for use in the United States

At this time, recipients of non-mRNA COVID-19 vaccines are not included. While the Janssen COVID-19 vaccine is authorized for use, as of this writing, there currently is an insufficient number of case-patients who have received the Janssen COVID-19 vaccine (i.e., v-safe registrants who reported systemic symptoms or health conditions resulting in medical attention including an emergency department visit or hospitalization on days 0–7 following the dose of Janssen COVID-19 vaccine) in the v-safe database to detect an effect based on the sample size calculations provided in Table 1. Based on the results of the nested case-control study involving recipients of the Pfizer and Moderna COVID-19 mRNA vaccines, this assessment may be repeated with recipients of the Janssen COVID-19 vaccine and other COVID-19 vaccine products that become available, once the target case-patient sample size is reached.

Data handling and storage

Data for this project, consistent with all v-safe data, will be collected, managed, and housed on a secure server by Oracle. Through Health and Human Services (HHS), Oracle has donated IT services to any federal agency conducting COVID-19 related activities. Oracle is providing IT support for v-safe. All data will be stored, processed, and transmitted in accordance with the Federal Information Security Modernization Act (FISMA) and based on NIST standards. Data will be housed in Oracle Cloud Infrastructure (OCI) U.S. Government Cloud tenancy; the OCI U.S. government tenancy is Federal Risk and Authorization Management Program (FEDRAMP) approved (https://www.gsa.gov/technology/government-it-initiatives/fedramp).

Per Oracle's internal policies, Oracle staff will not be able to view any individualized survey data (including variables with personally identifiable information [PII]) but, rather, will have access to aggregate deidentified data for reporting. CDC will have "read" access to the individualized survey data, including PII, provided by Oracle. On a continuous basis (either daily or weekly), these survey data will be accessible to CDC through downloads from the CDC IT contractor's secure server. The v-safe system employs strict security measures appropriate for the level of sensitivity of the data. Data received by CDC will be stored on an internal secure CDC/ISO server and access will be limited to authorized personnel.

Data from all components of this project may be combined into a master data set behind the CDC firewall using unique identification numbers assigned at registration.

Preapproved CDC investigators and data managers, including CDC contractors, will be the only individuals with access to the full data. All electronic documents, data sets, and files relevant to the project will be stored in encrypted network folders with restricted access on CDC computers. The survey team at CDC will be primarily responsible for data management activities, including data extraction, documentation, and archival of a final data set for data sharing purposes. The archive will include the protocol, statistical programs, human subjects review documents, statistical output, analytical data sets, and manuscripts. It will clearly identify the permanent storage location for these files.

Human subjects considerations and confidentiality

This protocol will require human subjects determination at CDC. PII collected with v-safe will be used to contact v-safe participants. No PII will be included in any analyses, manuscripts, reports, or data sets shared through external data requests. Participation in the survey is completely voluntary. This activity presents minimal risk to participants as data are being collected for surveillance purposes. Use of participant data will not adversely affect participants' rights or welfare.

This project is both conducted and supported by CDC, which is authorized to monitor and investigate COVID-19 vaccine safety during the post-authorization/post-approval period. The project utilizes existing and prospective data to address and investigate COVID-19 vaccine safety among persons with and without a history of SARS-CoV-2 infection preceding COVID-19 vaccination. This project is being conducted solely for the purpose of providing timely information to inform and update clinical recommendations for vaccine administration in the context of the COVID-19 pandemic. All of the activities that are proposed for this project are directly related to the investigation of severe adverse events following COVID-19 vaccination.

Limitations and challenges

Limitations and challenges for this surveillance project include the following:

(1) We will rely on self-report for the collection of post-vaccination symptoms and their severity, as well as history of SARS-CoV-2 infection, symptoms, test type, and test date. While we may ask participants if we can confirm this information with medical or

laboratory testing records, we may be unable to access this information for all participants.

(2) Participants for this surveillance project will come from individuals enrolled in v-safe. People who choose to participate in v-safe might be different from those who decline.

Dissemination

Findings will be shared with various groups, including advisory committees (e.g., Advisory Committee on Immunization Practices COVID-19 Vaccine Safety Technical Assistance Sub-Group (VaST)). We also anticipate sharing findings with the scientific community and with the public through a manuscript published in a peer-reviewed journal and/or public report.

References

1. U.S. Food and Drug Administration. Pfizer-BioNTech COVID-19 Vaccine. February 18, 2021, Accessed February 18, 2021, https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine
2. U.S. Food and Drug Administration. Moderna COVID-19 Vaccine. February 18, 2021, Accessed February 18, 2021, https://www.fda.gov/emergency-preparedness-and-response/coronavirus- disease-2019-covid-19/moderna-covid-19-vaccine
3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine*. 2020/12/31 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577

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5. Krammer F, Srivastava K, Alshammary H, et al. Antibody Responses in Seropositive Persons after a Single Dose of SARS-CoV-2 mRNA Vaccine. *New England Journal of Medicine*. 2021;doi:10.1056/NEJMc2101667

Attachment 1: Script and survey

Script

Script used when sending text message to selected cases and controls:

Initial text message: "Hi [NAME]. Thanks for your v-safe check-ins. We have a question about interest in a quick follow-up v-safe survey:" (link to survey) [103 characters with spaces]

Reminder text message: "Hi [NAME]. Please remember that we have a quick follow-up v-safe survey for you:" (link to survey) [69 characters with spaces]

After clicking on link, this script will be used to introduce the project:

"Hi [NAME]. We are contacting people who enrolled in v-safe to ask if they would be willing to answer a few additional questions. Answers to these questions will help us learn if people who had COVID-19 before they were vaccinated experienced more severe symptoms after receiving the vaccine than people who did not have COVID-19 before they were vaccinated. It should take about 5 minutes to answer all questions.

Would you be interested in participating in this project by answering a few questions?"

Yes [Continue to survey.]

No ["Thank you." Exit survey.]

Survey instrument

Thank you for participating. First, we'll ask questions about if you received a positive test for COVID-19 and, if so, what symptoms you experienced.
Question 1 Have you **ever** received a positive COVID-19 test result? This could have been a blood test, or a test that used specimens from your nose or your mouth (saliva). Yes No [Skip to Question 2]
Question 1b Have you **ever** received a positive result from a viral COVID-19 test? A viral test checks specimens from your nose or your mouth (saliva) to find out if you are currently infected with SARS-CoV-2, the virus that causes COVID-19. Yes No [Skip to Question 1j]
Question 1c Approximately when did you receive your **first positive** viral COVID-19 test result? If you do not know the exact day, select the first day of the month you were tested. List the date of the first positive result if you've had more than one. Month, Day, and Year options [If equal to December 2020, January 2021, February 2021, March 2021, April 2021, or May 2021: Did this test happen **before** you received the first dose of the COVID-19 vaccine? Yes No]
Question 1d Do you know the type of viral test used? (check all that apply) Nucleic acid amplification test (such as a PCR test) [Skip to Question 1g] Antigen test (rapid test) I don't know
Question 1e Have you **ever** received a positive nucleic acid amplification test (such as a PCR test)? Yes No [Skip to Question 1g] I don't know [Skip to Question 1g]
Question 1f Approximately when did you receive your **first positive** nucleic acid amplification test (such as a PCR test) result? If you do not know the exact day, select the first day of the month you were tested. List the date of the first positive result if you've had more than one. Month, Day, and Year options [If equal to December 2020, January 2021, February 2021, March 2021, April 2021, or May 2021: Did this test happen **before** you received the first dose of the COVID-19 vaccine? Yes No]
Question 1g What symptoms did you experience, if any, during your COVID-19 illness? (check all that apply)

Question 1g, continued

Fever or chills
Cough
Shortness of breath or difficulty breathing
Fatigue
Muscle or body aches
Headache
New loss of taste or smell
Sore throat
Congestion or runny nose
Nausea or vomiting
Diarrhea
Other, describe: [text box for entering other symptoms – limit to 250 characters with spaces]
I do not remember.
I did not have any symptoms. [Skip to Question 1j]

Question 1h

Did you get care from a doctor or other healthcare provider for your COVID-19 symptoms?

Yes
No [Skip to Question 1j]

Question 1i

Where did you get medical care for your COVID-19 symptoms? (check all that apply)

Telehealth, virtual health, or email health consultation
Doctor's office, outpatient clinic, or urgent care clinic visit
Emergency room or emergency department visit
Hospitalization
Other, describe: [text box for entering other medical care visits – limit to 250 characters with spaces]

Question 1j

Have you **ever** received a positive result from a COVID-19 antibody test? Antibody or serology tests look for antibodies in your blood to determine if you had a past infection with the virus that causes COVID-19.

Yes
No [Skip to Question 2]

Question 1k

Approximately when did you receive your **first positive** COVID-19 antibody test result?
If you do not know the exact day, select the first day of the month you were tested. List the date of the first positive result if you've had more than one.

Month, Day, and Year options

[If equal to December 2020, January 2021, February 2021, March 2021, April 2021, or May 2021: Did this test happen **before** you received the first dose of the COVID-19 vaccine? Yes No]

The following questions are specific to your **first** dose of the COVID-19 vaccine.
You may have answered these questions on a v-safe survey, but we need to confirm your information.

Question 2

During the 7 days after receiving the **first dose** of the COVID-19 vaccine, did you get care from a doctor or other healthcare provider for symptoms?

Yes
No [Skip to Question 3]

Question 2b

Where did you get medical care? (check all that apply)

Telehealth, virtual health, or email health consultation [If yes, "When was your telehealth, virtual health, or email health consultation? (list the date of the **first consultation** if you had more than one)" MM/DD/YYYY]

Doctor's office, outpatient clinic, or urgent care clinic visit [If yes, "When did you go to the doctor's office, outpatient clinic, or urgent care clinic? (list the date of the **first visit** if you had more than one)" MM/DD/YYYY]

Emergency room or emergency department visit [If yes, "When did you go to the emergency room or emergency department? (list the date of the **first visit** if you had more than one)" MM/DD/YYYY]

Hospitalization [If yes, "When were you hospitalized? (list the date of the **first hospitalization** if you had more than one)" MM/DD/YYYY]

Other, describe: [text box for entering other healthcare visits – limit to 250 characters with spaces] [If yes, "When did you get Other medical care?" MM/DD/YYYY]

Question 2c

What specific symptoms made you get care from a doctor or other healthcare provider? (check all that apply)

Pain at or near the injection site
Redness at or near the injection site
Swelling at or near the injection site
Itching at or near the injection site
Chills
Headache
Joint pain
Muscle or body aches
Fatigue or tiredness
Nausea
Vomiting
Diarrhea
Abdominal pain
Rash, not including the immediate area around the injection site
Other, describe: [text box for entering other symptoms – limit to 250 characters with spaces]

Finally, we'll ask some general questions about you.

Question 3

What is your race? (check all that apply)

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Pacific Islander
- White
- Other race
- Prefer not to answer

Question 4

What is your ethnic group?

- Hispanic or Latino
- Not Hispanic or Latino
- Prefer not to answer

Question 5

Has a doctor, nurse or other health professional ever told you that you had anaphylaxis after receiving a vaccine?

- Yes
- No
- I do not know

Question 6

Do you have any of the following medical conditions? (check all that apply)

- Cancer
- Chronic kidney disease
- Chronic lung disease, such as COPD (chronic obstructive pulmonary disease), asthma (moderate to severe), interstitial lung disease, cystic fibrosis, and pulmonary hypertension
- Dementia or other neurological conditions
- Diabetes (type 1 or type 2)
- Down syndrome
- Heart conditions, such as heart failure, coronary artery disease, cardiomyopathies, or hypertension
- HIV infection
- Immunocompromised state (weakened immune system)
- Liver disease
- Overweight and obesity (body mass index [BMI] > 25 kg/m2)
- Pregnancy
- Sickle cell disease or thalassemia
- Smoking (current or former)
- Solid organ or blood stem cell transplant
- Stroke or cerebrovascular disease
- Substance use disorders, such as alcohol, opioid, or cocaine use disorder
- Prefer not to answer
- None of these

Question 7

What is your occupation?

- Healthcare personnel
- First responder (e.g., firefighter and police officer)
- Corrections officer
- Food and agricultural worker
- U.S. Postal Service worker
- Manufacturing worker
- Grocery store worker
- Public transit worker
- Education sector (teacher or support staff member)
- Childcare worker
- Other, describe: [text box for specifying occupation – limit to 30 characters with spaces]
- Prefer not to answer
- Not currently employed

Question 8

Do you live in a long-term care facility, such as a skilled nursing facility, nursing home, or assisted living facility?

- Yes
- No
- Prefer not to answer

Onscreen completion thank you message:

"Thank you for completing this survey.
Depending on your answers, CDC may call you to get more information.
If you had symptoms or health problems following COVID-19 vaccination that concern you, please contact your healthcare provider. You can also report your experience to the Vaccine Adverse Event Reporting System (VAERS)."

Attachment 2

N/A indicates cell that will not be filled

Table 1. Characteristics of Participants, by Case-Control Status — v-safe, United States, December 14, 2020–May XX, 2021

N/A	No. (%)	No. (%)	N/A
Characteristic	Cases (n =)	Controls (n =)	*P* value
Age group, years	N/A	N/A	N/A
18–49	-	-	-
50–64	-	-	-
65–74	-	-	-
≥75	-	-	-
Sex	N/A	N/A	N/A
Female	-	-	-
Male	-	-	-
Other/Not specified	-	-	-
Race/Ethnicity	N/A	N/A	N/A
American Indian or Alaska Native, non-Hispanic	-	-	-
Asian, non-Hispanic	-	-	-
Black, non-Hispanic	-	-	-
Native Hawaiian or Pacific Islander, non-Hispanic	-	-	-
White, non-Hispanic	-	-	-
Hispanic	-	-	-
Other race, non-Hispanic	-	-	-
Occupation	N/A	N/A	N/A
Healthcare personnel	-	-	-
First responder (e.g., firefighter and police officer)	-	-	-
Corrections officer	-	-	-
Food and agricultural worker	-	-	-
U.S. Postal Service worker	-	-	-
Manufacturing worker	-	-	-
Grocery store worker	-	-	-
Public transit worker	-	-	-
Education sector (teacher or support staff member)	-	-	-
Childcare worker	-	-	-
Other	-	-	-
Not currently employed	-	-	-
Lives in a long-term care facility	N/A	N/A	N/A
No	-	-	-
Yes	-	-	-
Chronic underlying medical condition associated with increased risk for severe COVID-19[1]	N/A	N/A	N/A
0	-	-	-

≥ 1	-	-	-
Vaccine manufacturer	N/A	N/A	N/A
Moderna	-	-	-
Pfizer	-	-	-
History of anaphylaxis following vaccination	N/A	N/A	N/A
No	-	-	-
Yes	-	-	-
Positive SARS-CoV-2 test[2]	N/A	N/A	N/A
No	-	-	-
Yes, with confirmatory test	-	-	-
Yes, with presumptive test	-	-	-
Yes, with supportive test	-	-	-
Unsure	-	-	-
Months elapsed between COVID-19 diagnosis[3] and first COVID-19 vaccine dose, (n = # with positive test)	N/A	N/A	N/A
0–1	-	-	-
2–3	-	-	-
4–6	-	-	-
>6	-	-	-
Symptomatic COVID-19[3], (n = # with positive test)	N/A	N/A	N/A
No	-	-	-
Yes	-	-	-
COVID-19 severity[3], (n = # with symptomatic COVID)	N/A	N/A	N/A
Did not require medical attention	-	-	-
Medical attention via telehealth, virtual health, or email health consultation	-	-	-
Medical attention from outpatient clinic or urgent care clinic	-	-	-
Medical attention from emergency department	-	-	-
Hospitalized	-	-	-

[1]Defined using CDC's list of medical conditions that put people at increased risk for severe COVID-19: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
[2]Defined using the Council of State and Territorial Epidemiologists (CSTE) laboratory criteria: https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/08/05/
[3]Restricted to participants with positive confirmatory/nucleic acid amplification test results
Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification

Table 2. Unadjusted and Adjusted Associations Between History of SARS-CoV-2 Infection and Select Covariates and Severe Adverse Events Following Receipt of mRNA COVID-19 Vaccine — v-safe, United States, December 14, 2020–May XX, 2021

N/A	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex	N/A	N/A
Female	Ref	Ref
Male	-	-
Race/Ethnicity	N/A	N/A
White, non-Hispanic	Ref	Ref
American Indian or Alaska Native, non-Hispanic	-	-
Asian, non-Hispanic	-	-
Black, non-Hispanic	-	-
Native Hawaiian or Pacific Islander, non-Hispanic	-	-
Hispanic	-	-
Other race, non-Hispanic	-	-
Vaccine manufacturer	N/A	N/A
Moderna	Ref	Ref
Pfizer	-	-
History of anaphylaxis following vaccination	N/A	N/A
No	Ref	Ref
Yes	-	-
History of laboratory confirmed SARS-CoV-2 infection[1]	N/A	N/A
No	Ref	Ref
Yes	-	-

[1]Defined using the Council of State and Territorial Epidemiologists (CSTE) laboratory criteria: https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/08/05/

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2