



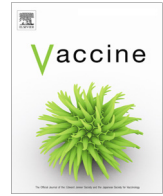
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Association between history of SARS-CoV-2 infection and severe systemic adverse events after mRNA COVID-19 vaccination among U.S. adults

Lindsay K. Tompkins^{a,b,*}, James Baggs^b, Tanya R. Myers^b, Julianne M. Gee^b, Paige L. Marquez^b, Sharon B. Kennedy^c, David Peake^c, Dhruv Dua^c, Anne M. Hause^b, Penelope Strid^b, Winston Abara^b, Rebecca Rossetti^b, Tom T. Shimabukuro^b, David K. Shay^b

^a Epidemic Intelligence Service, Center for Surveillance, Epidemiology and Laboratory Services, Centers for Disease Control and Prevention, Atlanta, GA, United States

^b CDC COVID-19 Response Team, Centers for Disease Control and Prevention, Atlanta, GA, United States

^c Oracle Corporation, Austin, TX, United States

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ABSTRACT

Background: Risk of experiencing a systemic adverse event (AE) after mRNA coronavirus disease 2019 (COVID-19) vaccination may be greater among persons with a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; data on serious events are limited. We assessed if adults reporting systemic AEs resulting in emergency department visits or hospitalizations during days 0–7 after mRNA COVID-19 vaccine dose 1 were more likely to have a history of prior SARS-CoV-2 infection compared with persons who reported no or non-severe systemic AEs.

Methods: We conducted a nested case-control study using v-safe surveillance data. Participants were ≥ 18 years and received dose 1 during December 14, 2020–May 9, 2021. Cases reported severe systemic AEs 0–7 days after vaccination. Three controls were frequency matched per case by age, vaccination date, and days since vaccination. Follow-up surveys collected SARS-CoV-2 histories.

Results: Follow-up survey response rates were 38.6 % (potential cases) and 56.8 % (potential controls). In multivariable analyses including 3,862 case-patients and 11,586 controls, the odds of experiencing a severe systemic AE were 2.4 (Moderna, mRNA-1273; 95 % confidence interval [CI]: 1.89, 3.09) and 1.5 (Pfizer-BioNTech, BNT162b2; 95 % CI: 1.17, 2.02) times higher among participants with pre-vaccination SARS-CoV-2 histories compared with those without. Medical attention of any kind for symptoms during days 0–7 following dose 2 was not common among case-patients or controls.

Conclusions: History of SARS-CoV-2 infection was significantly associated with severe systemic AEs following dose 1 of mRNA COVID-19 vaccine; the effect varied by vaccine received. Most participants who experienced severe systemic AEs following dose 1 did not require medical attention of any kind for symptoms following dose 2. Vaccine providers can use these findings to counsel patients who had pre-vaccination SARS-CoV-2 infection histories, experienced severe systemic AEs following dose 1, and are considering not receiving additional mRNA COVID-19 vaccine doses.

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1. Introduction

Two mRNA coronavirus disease 2019 (COVID-19) vaccines are available for administration in the United States, BNT162b2 manufactured by Pfizer-BioNTech [1] and mRNA-1273 manufactured by Moderna [2]. Clinical trials of these vaccines excluded persons with

a history of COVID-19 [3,4], limiting our understanding of the risk of adverse events in this population. Because of delays in baseline severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test results, some clinical trial participants who tested SARS-CoV-2 positive at trial entry received vaccine; information on this population of participants was reported for the mRNA-1273 clinical trial and suggested that incidence of systemic adverse reactions following dose 1 of mRNA-1273 vaccine was greater among participants who were SARS-CoV-2 positive at baseline (based on immunologic or virologic evidence) compared with those who

* Corresponding author at: Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30329, United States.

E-mail address: ltompkins@cdc.gov (L.K. Tompkins).

were SARS-CoV-2 negative [3]. mRNA-1273 clinical trial data also suggested that vaccine recipients who were SARS-CoV-2 negative at baseline had a greater incidence of local adverse reactions following dose 1 and both local and systemic adverse reactions following dose 2 compared to those who were SARS-CoV-2 positive at baseline [3].

The relationship between history of SARS-CoV-2 infection and adverse events following mRNA COVID-19 vaccination has been further studied since these vaccines were authorized. Enhanced systemic reactivity [5,6] and increased likelihood of clinically significant symptoms [7] among those with prior SARS-CoV-2 infection following dose 1 of mRNA COVID-19 vaccine have been reported. These data suggest that the risk of systemic reactions after dose 1 may be greater among persons with a history of SARS-CoV-2 infection than among immunologically naïve persons. Limited data are available on whether the risk of severe adverse events, including those resulting in an emergency department visit or hospitalization, might be higher among vaccinated persons with a history of a prior SARS-CoV-2 infection.

We aimed to determine if persons who reported experiencing severe systemic adverse events (i.e., resulting in an emergency department visit or hospitalization) to the U.S. Centers for Disease Control and Prevention's (CDC) v-safe safety monitoring system during days 0–7 following receipt of dose 1 of mRNA COVID-19 vaccine were more likely to have had a positive SARS-CoV-2 test prior to vaccination compared with persons who reported non-severe (i.e., not requiring medical attention) or no systemic adverse events. We hypothesized that risk of severe systemic reactivity would differ by pre-vaccination SARS-CoV-2 infection history.

2. Methods

V-safe active surveillance system for COVID-19 vaccination

In December 2020, CDC launched a voluntary, smartphone-based active surveillance system to monitor health status of U.S. residents who received COVID-19 vaccines. V-safe registrants receive text messages with links to web-based health surveys beginning on the day of first vaccination (day 0) through 12 months after the last dose of COVID-19 vaccine. During days 0–7 after each vaccine dose, participants are asked to report local and systemic signs and symptoms through daily surveys. The health impacts of reported signs and symptoms (i.e., inability to work or attend school, inability to do normal daily activities, required care from a doctor or other healthcare professional) are requested. If medical attention is reported, registrants are asked to specify the setting of healthcare visit (i.e., telehealth, virtual health, or email health consultation; outpatient clinic or urgent care clinic visit; emergency room or emergency department visit; hospitalization; other). Detailed v-safe procedures and policies are available [8].

Study design

We conducted a nested case-control study using v-safe data collected from enrolled registrants. Eligibility criteria for participation included age ≥ 18 years and receipt of dose 1 of an mRNA COVID-19 vaccine from December 14, 2020 through May 9, 2021. We excluded registrants who reported pregnancy and those who requested modifications to their v-safe data (e.g., requested a correction to their vaccination date). To allow all eligible registrants the opportunity to reply to v-safe surveys of interest, we collected data from day 0–7 surveys through May 16, 2021. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy. (See e.g., 45C.F.R. part 46.102(l)(2), 21C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.)

Case, control, and exposure definitions

Case-patients were defined as participants who reported systemic symptoms resulting in an emergency department visit or hospitalization (severe systemic adverse event) during days 0–7

following dose 1 of an mRNA COVID-19 vaccine, the outcome of interest.

Eligible controls were participants who: (1) were the same age (in years) as a corresponding case-patient upon receipt of dose 1 (all participants aged ≥ 90 years were treated as the same age); (2) were vaccinated within 3 days of a corresponding case-patient's vaccination date; (3) completed a health check-in survey on the same survey day that a corresponding case-patient reported an emergency department visit or hospitalization (i.e., same number of days since vaccination); (4) were non-cases on the day that a corresponding case-patient reported an emergency department visit or hospitalization; and (5) had no prior reports of seeking medical attention, including care via telehealth, outpatient/urgent care center, emergency department, or hospitalization, following dose 1. Additional details regarding matching criteria are available in the Supplementary material. Consistent with our study design, we allowed a registrant to be selected as a control for multiple case-patients, and we allowed a registrant to be selected as a control prior to meeting the case definition [9,10].

The exposure of interest was a history of laboratory-confirmed SARS-CoV-2 infection preceding vaccination. Information on pre-vaccination SARS-CoV-2 history was not collected through v-safe health surveys; therefore, a separate text message with a link to a web-based survey was sent to participants to obtain this information (described in *Data collection* section).

Participant recruitment

Potential case-patients and controls were contacted using telephone numbers provided during v-safe registration. Text messages were used to invite eligible v-safe registrants to participate in the study; a link to the web-based study survey was provided in the message. Potential participants received an initial invitation message and one reminder message, if needed. Text messages were sent on a rolling basis from May 10, 2021 through June 11, 2021.

Case-patients were recruited first. All potential case-patients were invited to participate. Potential controls were then randomly selected and recruited for each participating case-patient. Controls were oversampled by a multiplier of four. We attempted to match three controls per case. If three controls were not recruited for a case-patient after initial and reminder messages were sent, we recruited additional controls. If control participation for a given case exceeded the target, we randomly selected three controls to include in our analysis.

Data collection

If potential case-patients and controls agreed to participate in the study, they were directed to the study's web-based survey to respond to questions on self-reported history of a positive SARS-CoV-2 test result, date of positive test, type of test (i.e., nucleic acid amplification test [NAAT], antigen test, or antibody test), COVID-19 symptoms and medical attention sought for symptoms, race, ethnicity, occupation, residence in a long-term care facility, underlying medical conditions, and history of anaphylaxis following vaccination (see Supplementary material for questionnaire items). Findings regarding history of anaphylaxis following vaccination are not presented here but are available in the Supplementary material. Surveys were available in languages supported by v-safe (English, Spanish, Simplified Chinese, Korean, and Vietnamese).

We extracted the following data from the v-safe database for all case-patients and controls: age at vaccination, sex, vaccination date, dose number, vaccine received, symptoms reported during v-safe health surveys, the health impact of symptoms reported (including setting where medical care was received, if applicable), and pregnancy status.

Positive SARS-CoV-2 test result verification

We contacted subsets of participants who reported testing positive for SARS-CoV-2 prior to vaccination on the study survey. One

subset included those who reported a positive viral SARS-CoV-2 test but did not report the test type (i.e., NAAT or antigen); we contacted all these participants by phone to determine the type of test received. For a sensitivity analysis, we also contacted a 20 % random sample of participants who reported a positive viral SARS-CoV-2 test and provided the test type to verify the information reported. Detailed outreach and verification methods are described in the Supplementary material.

Data analysis

Primary analysis

We described demographic information, past SARS-CoV-2 infection characteristics, and medical setting where care was sought for symptoms following dose 1 of mRNA COVID-19 vaccine by case-control status. We used conditional logistic regression to estimate the association between history of SARS-CoV-2 infection detected using a confirmatory test (i.e., a NAAT) preceding vaccination and severe systemic adverse events during the 7 days following receipt of dose 1 of mRNA COVID-19 vaccine. We excluded participants who reported a history of a positive SARS-CoV-2 test with other (i.e., antigen or antibody tests) or unknown test types. We calculated crude and adjusted odds ratios (ORs) and 95 % confidence intervals (CIs). We tested for effect modification between SARS-CoV-2 history and vaccine received, using $P < .05$ to establish statistical significance. Adjusted results controlled for sex and race/ethnicity. Additional variables considered for inclusion in the adjusted model were occupation, residence in a long-term care facility, and chronic underlying medical condition associated with increased risk for severe COVID-19 [11]. We used a hierarchical backward elimination approach when building the adjusted model [12]. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

Secondary analyses

We repeated our primary analysis using an exposure variable that further categorized SARS-CoV-2 history by time (in days) between SARS-CoV-2 infection and receipt of dose 1 (categories: no history of infection, ≤ 30 , 31–90, 91–180, or > 180 days from infection to dose 1).

We also described medical attention sought for symptoms following dose 2 by case-control status and pre-vaccination SARS-CoV-2 history for participants who reported receiving dose 2 of an mRNA vaccine to v-safe and responded to at least one 0–7-day survey following dose 2. V-safe dose 2 data from December 14, 2020 through January 16, 2022 were used for this analysis.

Sensitivity analysis

To assess the reliability of self-reported test information, we described agreement between self-reported SARS-CoV-2 test result information and information collected from test result reports during phone follow-up.

3. Results

From December 14, 2020 through May 16, 2021, 10,004 v-safe registrants met the participation criteria and the case definition, from a total of 6,544,085 eligible participants. Therefore, the absolute risk of a reported severe systemic adverse event in this population was 15.3 per 10,000 (see Supplementary material for additional information). Response rates among potential case-patients and controls were 38.6 % and 56.8 %, respectively. Participants included 3,862 case-patients and 11,586 controls. There were 15,408 unique participants; four participants served as both controls and case-patients and 36 participants served as controls for more than one case-patient.

Characteristics of participants by case-control status

Characteristics of participants by case-control status are shown in Table 1. Three-quarters (74.5 %) of case-patients were female compared with 62.3 % of controls. Overall, case-patients and con-

Table 1

Characteristics of Participants by Case-Control Status — v-safe, United States, December 14, 2020–May 16, 2021.

Characteristic	No. (%)	
	Cases (n = 3862) ^a	Controls (n = 11 586) ^{a, b}
Age group, years		
18–49	1882 (48.7)	5646 (48.7)
50–64	1177 (30.5)	3531 (30.5)
65–74	575 (14.9)	1725 (14.9)
≥ 75	228 (5.9)	684 (5.9)
Sex		
Female	2878 (74.5)	7223 (62.3)
Male	941 (24.4)	4258 (36.8)
Other/Not specified	43 (1.1)	105 (0.9)
Race/Ethnicity		
Hispanic	412 (10.7)	1168 (10.1)
American Indian/Alaska Native or Native Hawaiian/Pacific Islander, non-Hispanic	32 (0.8)	70 (0.6)
Asian, non-Hispanic	144 (3.7)	592 (5.1)
Black, non-Hispanic	365 (9.5)	663 (5.7)
White, non-Hispanic	2637 (68.3)	8442 (72.9)
Other race, non-Hispanic	29 (0.8)	53 (0.5)
Multiple races, non-Hispanic	97 (2.5)	215 (1.9)
Not specified	146 (3.8)	383 (3.3)
Occupation		
Healthcare personnel	1072 (27.8)	2734 (23.6)
Non-healthcare frontline worker ^c	550 (14.2)	1905 (16.4)
Other occupation	1041 (27.0)	3768 (32.5)
Not currently employed	1076 (27.9)	2790 (24.1)
Prefer not to answer	123 (3.2)	389 (3.4)
Long-term care facility resident		
Yes	12 (0.3)	21 (0.2)
No	3842 (99.5)	11 540 (99.6)
Prefer not to answer	8 (0.2)	25 (0.2)
Chronic underlying medical condition associated with increased risk for severe COVID-19 ^d		
0	1405 (36.4)	5596 (48.3)
1	1155 (29.9)	3525 (30.4)
≥ 2	1274 (33.0)	2369 (20.5)
Prefer not to answer	28 (0.7)	96 (0.8)
Vaccine received		
mRNA-1273 (Moderna)	1935 (50.1)	5717 (49.3)
BNT162b2 (Pfizer-BioNTech)	1927 (49.9)	5869 (50.7)
Month vaccine dose 1 received		
December 2020	545 (14.1)	1646 (14.2)
January 2021	986 (25.5)	2946 (25.4)
February 2021	630 (16.3)	1887 (16.3)
March 2021	971 (25.1)	2932 (25.3)
April 2021	676 (17.5)	2012 (17.4)
May 2021	54 (1.4)	163 (1.4)

Abbreviations: COVID-19, coronavirus disease 2019.

^a 4 participants served as both cases and controls.

^b 11,550 unique controls.

^c Defined using The Advisory Commiwww.cdc.gov/coronavirustee on Immunization Practices' Updated Interim Recommendations for Allocation of COVID-19 Vaccine — United States, December 2020: <https://www.cdc.gov/mmwr/volumes/69/wr/mm695152e2.htm>.

^d Defined using CDC's list of medical conditions that put people at increased risk for severe COVID-19, excluding pregnancy: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>.

controls were similar by race/ethnicity; however, non-Hispanic Black participants were more likely to be case-patients (9.5 %) than controls (5.7 %) while non-Hispanic White participants were less likely to be case-patients (68.3 %) than controls (72.9 %). Chronic underlying medical conditions associated with increased risk for severe COVID-19 were more often reported by case-patients (62.9 %) than controls (50.9 %). Receipt of BNT162b2 or mRNA-1273 vaccine did not differ by case-control status.

Pre-vaccination SARS-CoV-2 history

Most participants did not report receiving a positive SARS-CoV-2 test result prior to mRNA COVID-19 vaccination (90.1 % of case-

Table 2
SARS-CoV-2 History Prior to Dose 1 of an mRNA COVID-19 Vaccine, by Case-Control Status – v-safe, United States, December 14, 2020–May 16, 2021.

Characteristic	No. (%) overall	
	Cases (n = 3862) ^a	Controls (n = 11 586) ^{a,b}
Positive SARS-CoV-2 test prior to dose 1 of mRNA COVID-19 vaccine ^c		
No	3479 (90.1)	10 987 (94.8)
Yes, with confirmatory test	270 (7.0)	418 (3.6)
Yes, with presumptive test	61 (1.6)	103 (0.9)
Yes, with supportive test	17 (0.4)	27 (0.2)
Yes, with unknown test type	35 (0.9)	51 (0.4)
	No. (%) with positive confirmatory test	
	Cases (n = 270)	Controls (n = 418)
Time from positive SARS-CoV-2 test to dose 1 of mRNA COVID-19 vaccine		
≤ 30 days	32 (11.9)	27 (6.5)
31–90 days	74 (27.4)	137 (32.8)
91–180 days	77 (28.5)	159 (38.0)
> 180 days	87 (32.2)	95 (22.7)
Symptomatic SARS-CoV-2 infection prior to dose 1 of mRNA COVID-19 vaccine		
No	10 (3.7)	23 (5.5)
Yes	260 (96.3)	395 (94.5)
	No. (%) with positive confirmatory test and symptomatic SARS-CoV-2 infection	
	Cases (n = 260)	Controls (n = 395)
Highest level of medical attention sought for SARS-CoV-2 infection		
Did not require medical attention	100 (38.5)	246 (62.3)
Telehealth, outpatient, or other non-emergent care ^d	75 (28.8)	109 (27.6)
Emergency department visit or hospitalization	85 (32.7)	40 (10.1)

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

^a 4 participants served as both cases and controls.

^b 11,550 unique controls.

^c Defined using the Council of State and Territorial Epidemiologists (CSTE) laboratory criteria (<https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2020-08-05/>). Confirmatory laboratory evidence: Detection of severe acute respiratory syndrome coronavirus 2 ribonucleic acid (SARS-CoV-2 RNA) in a clinical specimen using a molecular amplification test; Presumptive laboratory evidence: Detection of SARS-CoV-2 by antigen test in a respiratory specimen; Supportive laboratory evidence: Detection of specific antibody in serum, plasma, or whole blood. If multiple positive test results were reported, we categorized using the strongest laboratory evidence based on the information provided, with Confirmatory laboratory evidence as the highest level, followed by Presumptive laboratory evidence, and then Supportive laboratory evidence.

^d Includes medical attention via telehealth, virtual health, email health consultation, outpatient clinic, urgent care clinic, and other medical care.

patients and 94.8 % of controls; Table 2). Greater proportions of case-patients reported a positive result with a confirmatory test (i.e., NAAT) than controls (7.0 % vs 3.6 %, respectively). Among those with positive confirmatory SARS-CoV-2 test results, the majority reported symptoms (96.3 % of case-patients and 94.5 % of controls). Case-patients more often reported receiving medical attention at an emergency department or being hospitalized for symptomatic SARS-CoV-2 infections than controls (32.7 % vs 10.1 %, respectively).

Association between SARS-CoV-2 infection history and severe systemic adverse events following dose 1 of an mRNA COVID-19 vaccine

In multivariable analyses adjusted for sex and race/ethnicity and matched on age, vaccination date, and v-safe survey, the odds of experiencing a severe systemic adverse event following dose 1 of an mRNA COVID-19 vaccine were higher among participants with a history of a laboratory-confirmed SARS-CoV-2 infection before vaccination compared with those without a history of infection (Table 3). Effect modification was found between SARS-CoV-2 history and mRNA vaccine received ($P = .02$). The effect of history of SARS-CoV-2 was greater among those who received mRNA-1273 than among those who received BNT162b2 vaccine (adjusted odds ratio [aOR] mRNA-1273: 2.36, 95 % confidence interval [CI]: 1.84, 3.01, $P < .001$; aOR BNT162b2: 1.52, 95 % CI: 1.16, 2.00, $P = .003$).

Results of multivariable analyses estimating the association between time from laboratory-confirmed SARS-CoV-2 infection to dose 1 of mRNA COVID-19 vaccine and severe systemic adverse events during the 7 days following receipt of dose 1 are presented in Table 4. The effect was greatest among mRNA-1273 recipients with a history of laboratory-confirmed SARS-CoV-2 infection ≤ 30 days before dose 1 compared with mRNA-1273 recipients with no history of a positive SARS-CoV-2 test (aOR: 6.05, 95 % CI: 3.03, 12.10, $P < .001$).

Sensitivity analysis

Of the 138 participants contacted to verify self-reported positive SARS-CoV-2 test result details, 67 (48.6 %) participated and provided reports of their test result for verification. For most participants (95.5 %), self-reported test type was concordant with the test type listed on the test report (Supplementary Table 1). In all instances where disagreement was noted ($n = 3$), participants self-reported that the test type was an antigen test, while the test result report indicated that it was a NAAT. When assessing differences in test date, 92.5 % of participants self-reported test dates that were within 3 days of the specimen collection date listed on the result report.

Medical attention received after dose 2

Overall, 13,232 (85.7 %) study participants reported dose 2 of an mRNA COVID-19 vaccine to v-safe and responded to at least one health survey during days 0–7 post-vaccination (by case-control status: 70.6 % of cases, 90.7 % of controls). The majority of case-patients and controls who responded to v-safe surveys after dose 2 did not report seeking care for symptoms (93.6 % and 99.7 %, respectively; Table 5), though medical attention was more frequently reported by case-patients than controls (6.4 % vs 0.3 %, respectively; $P < .001$).

Sixty-seven participants (0.5 %) reported an emergency department visit or hospitalization following dose 2 associated with post-vaccination symptoms. Of the 64 case-patients who reported an emergency department visit or hospitalization after dose 2, two reported a pre-vaccination positive confirmatory SARS-CoV-2 test, two reported a pre-vaccination positive SARS-CoV-2 test of unknown type, and the remaining 60 reported no pre-vaccination SARS-CoV-2 history. Of the three controls who reported an emergency department visit or hospitalization after dose 2, none reported a pre-vaccination SARS-CoV-2 history.

4. Discussion

During the study period, reports of severe systemic adverse events, defined as systemic adverse events resulting in an emergency department visit or hospitalization, to v-safe during days 0–7 following receipt of dose 1 of mRNA COVID-19 vaccine were rare. Consistent with findings from prior reports about systemic reactions following dose 1 of mRNA COVID-19 vaccine among persons with prior SARS-CoV-2 infection [3,5–7], we found that a history of SARS-CoV-2 infection was associated with more frequent reports of severe systemic adverse events following dose 1. This

Table 3

Associations between history of laboratory confirmed SARS-CoV-2 infection before receipt of an mRNA COVID-19 vaccine and select covariates and severe systemic adverse events following vaccine dose 1 – v-safe, United States, December 14, 2020–May 16, 2021.

	Unadjusted OR (95 % CI) ^a	Adjusted OR (95 % CI) ^a
History of laboratory confirmed SARS-CoV-2 infection ^{b,c}		
No	Ref	Ref
Yes; Vaccine received: BNT162b2 (Pfizer-BioNTech)	1.56 (1.19, 2.04) †	1.52 (1.16, 2.00) †
Yes; Vaccine received: mRNA-1273 (Moderna)	2.43 (1.91, 3.09) ‡	2.36 (1.84, 3.01) ‡
Sex		
Male	Ref	Ref
Female	1.83 (1.68, 1.99) ‡	1.80 (1.65, 1.96) ‡
Other/Unknown	1.93 (1.34, 2.78) ‡	1.89 (1.31, 2.73) ‡
Race/Ethnicity		
White, non-Hispanic	Ref	Ref
Hispanic	1.12 (0.99, 1.27)	1.11 (0.98, 1.26)
American Indian/Alaska Native or Native Hawaiian/Pacific Islander, non-Hispanic	1.39 (0.89, 2.16)	1.47 (0.94, 2.30)
Asian, non-Hispanic	0.81 (0.67, 0.98) *	0.86 (0.71, 1.04)
Black, non-Hispanic	1.75 (1.52, 2.01) ‡	1.68 (1.46, 1.94) ‡
Other race, non-Hispanic	1.82 (1.14, 2.90) *	2.06 (1.28, 3.32) †
Multiple races, non-Hispanic	1.51 (1.18, 1.93) †	1.47 (1.15, 1.89) †
Not specified	1.21 (0.99, 1.48)	1.28 (1.04, 1.57) *

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

* $P < .05$; † $P < .01$; ‡ $P < .001$.

^a Cases and controls matched on age, vaccination date, and v-safe survey.

^b 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/>. Confirmatory laboratory evidence: Detection of severe acute respiratory syndrome coronavirus 2 ribonucleic acid (SARS-CoV-2 RNA) in a clinical specimen using a molecular amplification test. Participants with presumptive (i.e., positive antigen test) or supportive (i.e., positive antibody test) evidence, as well as those with positive tests of unknown type, were excluded.

^c Likelihood ratio test comparing adjusted model without interaction term to adjusted model with interaction term: Deviance difference: 5.466, degrees of freedom: 1, $P = .02$.

Table 4

Associations Between Time from Laboratory Confirmed SARS-CoV-2 Infection to Receipt of Dose 1 of an mRNA COVID-19 Vaccine and Select Covariates and Severe Systemic Adverse Events – v-safe, United States, December 14, 2020–May 16, 2021.

	Unadjusted OR (95 % CI) ^a	Adjusted OR (95 % CI) ^a
Time between laboratory confirmed SARS-CoV-2 infection and dose 1 ^{b,c,d}		
None (no history of laboratory confirmed infection)	Ref	Ref
≤ 30 days; vaccine: BNT162b2	1.75 (0.73, 4.17)	1.93 (0.80, 4.67)
31–90 days; vaccine: BNT162b2	1.14 (0.73, 1.80)	1.10 (0.69, 1.73)
91–180 days; vaccine: BNT162b2	1.48 (0.99, 2.21)	1.42 (0.95, 2.14)
> 180 days; vaccine: BNT162b2	2.28 (1.50, 3.48) ‡	2.25 (1.47, 3.46) ‡
≤ 30 days; vaccine: mRNA-1273	5.70 (2.89, 11.23) ‡	6.05 (3.03, 12.10) ‡
31–90 days; vaccine: mRNA-1273	2.32 (1.59, 3.39) ‡	2.25 (1.53, 3.30) ‡
91–180 days; vaccine: mRNA-1273	1.67 (1.14, 2.44) †	1.56 (1.06, 2.31) *
> 180 days; vaccine: mRNA-1273	3.98 (2.58, 6.14) ‡	3.83 (2.47, 5.96) ‡
Sex		
Male	Ref	Ref
Female	1.83 (1.68, 1.99) ‡	1.81 (1.66, 1.97) ‡
Other/Unknown	1.93 (1.34, 2.78) ‡	1.94 (1.34, 2.80) ‡
Race/Ethnicity		
White, non-Hispanic	Ref	Ref
Hispanic	1.12 (0.99, 1.27)	1.10 (0.96, 1.24)
American Indian/Alaska Native or Native Hawaiian/Pacific Islander, non-Hispanic	1.39 (0.89, 2.16)	1.45 (0.93, 2.27)
Asian, non-Hispanic	0.81 (0.67, 0.98) *	0.85 (0.70, 1.03)
Black, non-Hispanic	1.75 (1.52, 2.01) ‡	1.66 (1.44, 1.91) ‡
Other race, non-Hispanic	1.82 (1.14, 2.90) *	2.12 (1.32, 3.40) †
Multiple races, non-Hispanic	1.51 (1.18, 1.93) †	1.48 (1.15, 1.90) †
Not specified	1.21 (0.99, 1.48)	1.27 (1.04, 1.56) *

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

* $P < .05$; † $P < .01$; ‡ $P < .001$.

^a Cases and controls matched on age, vaccination date, and v-safe survey.

^b Laboratory confirmed SARS-CoV-2 infection 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/>. Confirmatory laboratory evidence: Detection of severe acute respiratory syndrome coronavirus 2 ribonucleic acid (SARS-CoV-2 RNA) in a clinical specimen using a molecular amplification test. Participants with presumptive (i.e., positive antigen test) or supportive (i.e., positive antibody test) evidence, as well as those with positive tests of unknown type, were excluded.

^c Likelihood ratio test comparing adjusted model without interaction term to adjusted model with interaction term: Deviance difference: 12.405, degrees of freedom: 4, $P = .02$.

^d Likelihood ratio test comparing adjusted model when using time between laboratory confirmed SARS-CoV-2 infection and dose 1 mRNA COVID-19 vaccine variable with adjusted model when using history of laboratory confirmed SARS-CoV-2 infection (as presented in Table 3): Deviance difference: 44.725, degrees of freedom: 6, $P < .001$.

Table 5

Medical Attention Sought for Symptoms Following Dose 2 of an mRNA COVID-19 Vaccine by Case-Control Status – v-safe, United States, December 14, 2020–January 16, 2022.

Characteristic	No. (%)		P value
	Cases (n = 2726)	Controls (n = 10 506)	
Highest level of medical attention sought for symptoms following dose 2			
Did not require medical attention	2551 (93.6)	10 475 (99.7)	<.001
Telehealth, outpatient, or other non-emergent care ^a	111 (4.1)	28 (0.3)	
Emergency department visit or hospitalization	64 (2.3)	3 (<0.1)	

Abbreviations: COVID-19, coronavirus disease 2019; mRNA, messenger RNA.

^a Includes medical attention via telehealth, virtual health, email health consultation, outpatient clinic, and urgent care clinic.

effect was significantly greater among those who received an mRNA-1273 versus a BNT162b2 vaccination, consistent with the general reactogenicity profiles of the two vaccines [13,14] and with the amount of mRNA in each (mRNA-1273, 100 µg [15]; BNT162b2, 30 µg [16]). When evaluating time between laboratory-confirmed SARS-CoV-2 infection and dose 1 of mRNA COVID-19 vaccine, the effect was greatest among mRNA-1273 recipients with an infection 30 or fewer days before dose 1.

Most case-patients and controls reported receiving dose 2 of mRNA COVID-19 vaccine and responded to at least one day 0–7 v-safe health survey after this dose. <7 % of case-patients reported seeking medical attention for symptoms following dose 2; only a small proportion (2.3 %) reported the same level of medical attention that they received after dose 1. These findings should be helpful to patients with a history of SARS-CoV-2 infection before vaccination who experienced a severe systemic adverse event following their first mRNA COVID-19 vaccine dose and who may be delaying or considering not receiving additional doses.

A strength of our study is that we used v-safe enrollment data to identify cases and controls. V-safe's large pool of registrants and information on post-vaccination symptom severity and health impact enabled us to explore more severe systemic adverse events than considered in other evaluations. Another strength is that participants were asked to respond to v-safe surveys daily during the post-vaccination time period of interest, limiting recall bias of symptoms experienced and medical attention sought for symptoms.

Our study is subject to limitations. Participation in v-safe is voluntary and represents < 5 % of vaccinated persons in the United States, limiting generalizability of our findings. Medical attention sought for signs and symptoms following vaccination was self-reported and not confirmed with review of medical records. In addition, not all v-safe registrants responded to every health survey. Surveys that were skipped could be related to the outcome of interest (i.e., emergency department visit or hospitalization). However, severe outcomes may have prompted some vaccine recipients to enroll in v-safe to report an adverse event. We also relied on self-report for the collection of SARS-CoV-2 infection history which may have resulted in exposure misclassification; however, our sensitivity analysis found substantial agreement between self-report and test result reports.

5. Conclusions

Reports of systemic adverse events resulting in a report of an emergency department visit or hospitalization were rare in v-safe. A history of SARS-CoV-2 infection before vaccination was

associated with severe systemic adverse events during days 0–7 following the first dose of an mRNA COVID-19 vaccine. The effect of prior SARS-CoV-2 infection was greater among mRNA-1273 recipients than among BNT162b2 recipients. Medical attention of any kind for symptoms during the days 0–7 following a second dose of an mRNA vaccine was not common among case-patients or controls. Vaccine providers can use these findings to counsel patients who had pre-vaccination SARS-CoV-2 infection histories, experienced severe systemic AEs following dose 1, and are delaying or considering not receiving additional mRNA COVID-19 vaccine doses. COVID-19 vaccine studies that include participants with a history of SARS-CoV-2 infection and collect data on immunological responses to SARS-CoV-2 infection and vaccination at study entry and following primary series and booster vaccinations may inform the development of future COVID-19 vaccines and the policies for their use.

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Data availability

The authors do not have permission to share data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2022.10.073>.

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