HHS Public Access

Author manuscript

*Sex Transm Dis*. Author manuscript; available in PMC 2025 August 01.

Published in final edited form as:

*Sex Transm Dis*. 2024 August 01; 51(8): 509–515. doi:10.1097/OLQ.0000000000001978.

# JYNNEOS vaccine safety surveillance during the 2022 mpox outbreak using the Vaccine Adverse Event Reporting System (VAERS) and v-safe, United States, 2022—2023

**Jonathan Duffy, MD, MPH**[1], **Tanya R. Myers, PhD, MPH**[1], **Paige Marquez, MSPH**[1], **Douglas Rouse, MD, MPH**[2], **Hannah Brown, FNP-C**[1], **Bicheng Zhang, MS**[1], **David K. Shay, MD, MPH**[1], **Pedro L. Moro, MD, MPH**[1]

[1]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA.

[2]Office of Biostatistics and Pharmacovigilance, Food and Drug Administration, Silver Spring, MD.

## Abstract

**Background:** In response to the 2022 mpox outbreak in the United States, people with higher potential for exposure to mpox were recommended to receive two doses of the JYNNEOS vaccine. Vaccine safety was monitored using two complementary systems.

**Methods:** The Vaccine Adverse Event Reporting System (VAERS) is a passive surveillance system that accepts reports of adverse events following vaccination. VAERS is capable of rapidly identifying rare adverse events and unusual reporting patterns. Medical records were requested and reviewed for adverse events of special interest, including myocarditis. Adverse event reporting rates were calculated as the number of verified adverse event cases divided by the number of JYNNEOS doses administered. V-safe for mpox was a voluntary smartphone-based vaccine safety surveillance system that sent enrolled persons text messages linked to health surveys asking about reactions and health impact events occurring after vaccination.

**Results:** There were 1,207,056 JYNNEOS doses administered in the United States. VAERS received 1,927 reports for JYNNEOS. The myocarditis reporting rate per million doses was 2.69 after dose 1 and 8.64 after dose 2. V-safe had 213 participants complete at least one health survey. Rates of injection site and systemic reactions were similar in the first week following dose 1 and dose 2.

**Conclusions:** JYNNEOS vaccine safety surveillance findings from VAERS and v-safe did not identify any unexpected safety concerns. The VAERS reporting rate for myocarditis was similar to previously published population background rates.

## Short Summary

Post-licensure and post-authorization vaccine safety monitoring of JYNNEOS during the 2022 U.S. mpox outbreak did not identify any unexpected safety concerns.

Correspondence: Jonathan Duffy, MD, MPH, MS H16-3, 1600 Clifton Rd., NE, Atlanta, GA 30329-4027, USA, jduffy@cdc.gov.

Disclaimer: The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Food and Drug Administration.

**Keywords**

mpox; smallpox vaccine; vaccine safety; adverse event; myocarditis

## BACKGROUND

In May 2022, a large multinational outbreak of mpox was identified.[1] Mpox is caused by the *Monkeypox virus*, which can be transmitted from person-to-person through close personal contact. Most mpox cases during the outbreak were associated with sexual contact and occurred in men who have sex with men.[1]

In response to the outbreak in the United States, the Centers for Disease Control and Prevention recommended vaccination against mpox for people with higher potential for exposure to mpox. This included men who have sex with men, transgender, or nonbinary persons, who had a new sexually transmitted disease or more than one sex partner in the prior six months; people who had sex at a commercial sex venue or in association with a large public event in the prior six months; sexual partners of people with the preceding risk factors; and people with HIV infection or other causes of immunosuppression who may be exposed to mpox.[2]

The vaccine used was JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-replicating; Bavarian Nordic, Denmark). JYNNEOS was approved by the Food and Drug Administration (FDA) in 2019 for use in people ≥18 years of age, administered as two 0.5mL doses 28 days apart by subcutaneous injection into the upper arm.[3] As the outbreak increased, the demand for JYNNEOS exceeded the available supply. To increase the number of doses available, the FDA issued an emergency use authorization (EUA) in August 2022 that allowed administration of 0.1mL doses by intradermal injection, which a previous study showed would produce a similar immune response to the standard dose.[4] The preferred body site for intradermal injection was the forearm, but CDC guidance also allowed injection in the upper arm or upper back.[2] The EUA also allowed for vaccination of individuals <18 years of age using the standard subcutaneous dose.

JYNNEOS is a third-generation smallpox vaccine. Older smallpox vaccines contain live, replicating vaccinia virus and are associated with risks of certain serious adverse reactions, including myocarditis and pericarditis. The biologic mechanism for the myopericarditis has not been determined but is thought to be immune mediated rather than a result of viral replication in the heart.[5] The safety of JYNNEOS was studied in prelicensure clinical trials in more than 7,800 adults and no cases of myocarditis or pericarditis were identified.[3] However, a theoretical concern remained that these conditions might occur at a lower rate than could be detected in the prelicensure studies.

The 2022 mpox outbreak led to the first large scale use of JYNNEOS outside of clinical trials. Vaccine safety is routinely monitored during post-licensure use of new vaccines, which may detect adverse events (AE) too rare to occur in clinical trials. Here we describe JYNNEOS post-licensure vaccine safety monitoring in the United States done using two complementary surveillance systems.

# METHODS

## Vaccine Adverse Event Reporting System (VAERS)

The first system is VAERS, which is a national passive surveillance system.[6] VAERS receives individual case safety reports that describe AEs, which are defined as any untoward medical occurrence in a person administered a vaccine, whether or not the event is caused by vaccination.[7] A report may contain information about more than one AE. AEs are reported as free text and coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.[6] The report of an AE to VAERS is not documentation that a vaccine caused the event. Anyone may submit a report to VAERS, and health care providers and vaccine manufacturers are required to report certain events. The 2022 JYNNEOS EUA required reporting of vaccine administration errors (whether or not associated with an AE), serious AEs (irrespective of attribution to vaccination), and cases of cardiac (including myocarditis and pericarditis), thromboembolic, and neurovascular events.[4] "Serious" is defined as events that result in death, a life-threatening event, hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.[6] Medical records (including death certificates and autopsy reports when applicable) were requested for serious AEs and pre-specified AEs of special interest, such as myocarditis and anaphylaxis, regardless of serious/non-serious classification.

Myocarditis and pericarditis case reports were classified using CDC case definitions, which are based on symptoms, signs, troponin, electrocardiogram, or cardiac imaging findings.[8] Myocarditis may be classified as probable or confirmed. The term myopericarditis is used when individuals meet criteria for both myocarditis and pericarditis. For analysis, cases were grouped as: 1) myocarditis with or without pericarditis, or 2) pericarditis alone. Previous surveillance activities for live, replicating smallpox vaccines included cases with symptom onset within 4–30 days after vaccination, but we included cases with symptom onset within 1–30 days after vaccination in the analysis to be more inclusive because JYNNEOS contains a non-replicating virus. The day of vaccination was defined as day 0. Anaphylaxis case reports were classified using the Brighton Collaboration case definition.[9]

To better characterize the contribution of vaccine administration errors to overall reporting, all reports were manually reviewed to classify whether each was reporting: 1) a vaccine administration error; 2) an adverse health event, defined as any sign or symptom in the person receiving the vaccine. Each report could contain one, both, or neither of these.

This analysis included reports received and processed from May 22, 2022, through March 31, 2023, with JYNNEOS entered on the VAERS form in either item 17 (vaccines received on the most recent vaccination date) or item 22 (other vaccines received within one month prior to the date for item 17). All reports were manually reviewed by the authors (JD and DR) as the reports were received.

Reporting rates were calculated by dividing the number of VAERS reports by the number of JYNNEOS doses administered from May 22, 2022, through March 24, 2023, which allowed a minimum of 7 days for VAERS reporting after the most recent doses. U.S. mpox vaccine

administration data were collected by jurisdictional Immunization Information Systems and reported to CDC by 61 jurisdictions (state, local, territorial).[10] Reporting rates were calculated for strata by sex, age group, route of administration, and dose number in series.

### V-safe

The second system is v-safe. From November 16, 2022 through March 21, 2023, CDC conducted active monitoring of AEs following JYNNEOS vaccination using v-safe, a voluntary smartphone-based U.S. vaccine safety surveillance system that used text messaging to initiate web-based surveys. V-safe originated in 2020 as a system specifically for COVID-19 vaccines. V-safe for mpox vaccines was not available during the first 6 months of JYNNEOS distribution due to the time needed to implement administrative and technical requirements. Participants in v-safe self-enrolled using the vsafe.cdc.gov website. Each participant submitted information about vaccines received (e.g., date of administration, other vaccines received on the same date) and health information (e.g., pregnancy and breastfeeding status, immunocompromised status). Participants were asked to indicate the anatomic location of vaccination for each dose (above the elbow, below the elbow, or back) as a proxy for subcutaneous or intradermal administration. We assumed administration was subcutaneous if the location was the arm above the elbow. Mpox vaccine doses reported as unknown vaccine name were assumed to be JYNNEOS.

V-safe participants received text messages that were timed relative to the most recent dose received and contained links to online health surveys. Survey frequency was daily during the first week of vaccination and then weekly up to day 42 after vaccination. Daily surveys asked questions about local reactions at the injection site (pain, redness, swelling, induration, rash, and itching), systemic reactions (chills, headache, joint pain, arthralgia, myalgia, fatigue, nausea, vomiting, diarrhea, abdominal pain, and non-local rash), and “other” symptoms. Weekly surveys asked participants whether they had experienced any new or worsening symptoms since their last health check-in. Surveys at days 21 and 28 included a question about subsequent diagnosis of myocarditis. The day 42 survey included questions about discoloration or scarring at the injection site. The survey is shown in Supplemental Digital Content 2.

If a participant reported symptoms, additional questions were asked about the severity of each symptom and whether the symptoms experienced caused any health impacts. Health impacts were defined as inability to work or attend school, inability to participate in normal daily activities, or seeking healthcare. Participants were asked to identify the source of healthcare received (telehealth, outpatient office or clinic, emergency room, hospitalization or other). Reports of healthcare prompted telephone outreach from the v-safe call center that encouraged completion of a VAERS report. Because v-safe for mpox vaccines was not available at the start of JYNNEOS distribution, participants registering more than 48 days after their last dose (after closure of the day 42 survey) received a short survey asking about health impacts; the call center could then follow-up on reports of medically attended symptoms. Data collection, flow and processing were conducted as previously described for COVID-19 vaccines.[11]

These activities were reviewed by CDC and conducted consistent with applicable federal law and CDC policy.[12]

## RESULTS

### Vaccine Adverse Event Reporting System

There were 1,207,056 JYNNEOS doses administered nationally during the analytic period. VAERS received 1,927 reports for JYNNEOS. The overall reporting rate was 1,596 reports per million doses administered.

JYNNEOS was reported on the most recent vaccination date (VAERS form item 17) for 1,901 (99%) reports and for a prior vaccination date only (item 22) for 26 (1%) reports. JYNNEOS was administered alone (without other vaccines on the same day) in 96% of reports. Most reports (77%) were in males, but the reporting rate was greater for females (Table 1).

Vaccine administration errors involving JYNNEOS were described in 959 reports (50%) and an adverse health event was described in 921 reports (48%). Most reports of an administration error did not include an adverse health event (931 [97%]). Regarding route of administration, errors were reported for intradermal injection at about three-times the rate for subcutaneous injection (Table 2). Intramuscular injection was also reported, usually as an error in route of administration. Types of errors more frequently reported for intradermal injection included inability to create a skin wheal on the first attempt (n=251) and vaccine leaking from the injection site (n=70). The adverse health event reporting rates were similar for all three routes of administration (Table 2). The most common types of adverse health events reported were injection site reactions (Table 3).

There were 34 serious reports, including four deaths. The causes of death reported by local authorities for three of the cases were: cocaine toxicity, drowning, and methamphetamine intoxication. The fourth case was a published report of death caused by mpox disease in a person vaccinated after the onset of skin lesions.[13] The most common condition among serious reports was myocarditis.

Seven cases of myocarditis were reported (two confirmed, five probable); three also met the definition of pericarditis. All cases were in males. Age ranged from 28 to 71 years (median 38). One case had onset of cardiac symptoms 62 days after the most recent dose of JYNNEOS and was excluded from further analysis. The day of symptom onset for the remaining cases is shown in Supplemental Figure 1. One of the cases was diagnosed with mpox disease after vaccination on the same day his chest pain started. Another case had a history of myocarditis ten years prior (cause not reported). Two cases received other vaccines on another day after JYNNEOS and before the onset of symptoms (one bivalent mRNA COVID-19 and one inactivated polio). Six cases were hospitalized; all survived. The reporting rate per million doses was 2.69 after dose 1 and 8.64 after dose 2 (Supplemental Table 1).

Five cases of pericarditis alone were reported; four in males. Age ranged from 26 to 57 years (median 39). All had symptom onset within seven days after vaccination (Supplemental Figure 1). Two cases had evidence of bacterial infection at the time of diagnosis. None received other vaccines. Two were hospitalized. All survived. The reporting rate per million doses was 5.38 after dose 1 and 2.16 after dose 2 (Supplemental Table 1).

Three cases of anaphylaxis were reported (all Brighton level 2); one case in a male, one in a female, and one with sex not reported. There were two cases after dose 1 for a reporting rate of 2.69 per million doses and one case after dose 2 for a rate of 2.16 per million doses. Other non-anaphylactic hypersensitivity reactions were also reported. Hives were reported for 30 people, including two with dermatographia. Urticaria was a frequently coded term for reports about intradermal injection, but many of these reports were referring to the skin wheal produced by intradermal injection or described swelling at the injection site using the word “welt”; those reports were not considered indicative of allergic reactions.

There were 94 cases of syncope confirmed by manual review. Ten indicated a fall occurred, of which six described a visible injury, including five with bruising or contusion and two with laceration. None were serious. By route of administration, there were 79 cases after intradermal injection (122 per million doses) and 11 after subcutaneous injection (30 per million doses).

There were 12 reports of scar formation at the injection site (route: eight intradermal, one subcutaneous, and three not reported). There were 32 reports of injection site discoloration (21 intradermal, three subcutaneous, one intramuscular, seven not reported).

There were 25 reports about adolescents. Adverse health events were one report of syncope and three reports of unspecified mild local and systemic reactogenicity. The other 21 reports were administration errors without an adverse health event, of which 18 were erroneous intradermal instead of subcutaneous administration. There were no VAERS reports about vaccination during pregnancy or breastfeeding.

### V-safe

During November 16, 2022 – March 21, 2023, 213 participants registered and completed at least one health survey. These participants were considered active participants; they completed 1,295 surveys. Demographic and other characteristics of these participants are shown in Table 4. Participant ages ranged from 18 through 79 years (median age at first dose, 41 years). A majority reported assignment of sex at birth as male (n=174, 81.7%) and current gender as male (n=166, 77.9%). Participants identified themselves as predominantly White, non-Hispanic. Nearly a fifth of participants (n=35, 16.4%) self-reported an immunocompromising condition or use of immunosuppressive medication at the time of vaccination. Active participants reported 213 first doses, of which 90 (42.3%) were classified as subcutaneous, and reported 166 second doses, of which 57 (34.3%) were classified as subcutaneous. Participants confirmed the mpox vaccine received was JYNNEOS for 349 (92%) of the total 379 doses reported, while they did not know the vaccine name for the remaining 30 (8%).

Less than half of the 213 active participants completed their initial survey in the first week after vaccination. A total of 59 participants completed surveys on days 0–7 after dose 1, and 71 participants completed surveys on days 0–7 after dose 2. A majority (n=32, 54.2%) reported their first dose as received above the elbow, presumed to represent subcutaneous administration. A minority (n=27, 38.0%) reported their second dose as received above the elbow. Participants reported injection site and systemic reactions with similar frequency in the first week following dose 1 and 2 (Figure 1). The most frequently reported local reactions were redness, itching, swelling, and induration; the most frequently reported systemic reactions were fatigue, myalgia, and headache (Supplemental Figure 2).

There were three reports of receiving medical care for symptoms experienced in the first week after dose 1 of JYNNEOS, two in a clinic setting after presumed intradermally administered vaccine and one “other” setting after subcutaneously administered vaccine. No participant reported medical care for symptoms in the first week after dose 2. No participant reported a diagnosis of myocarditis at day 21 or 28 after vaccination. Participants reported discoloration more frequently after dose 2 of presumed intradermally administered JYNNEOS (n=27, 52.9%) as compared to subcutaneously administered vaccine (n=5, 21.7%). There were a few reports of injection site scarring after dose 2: four after intradermal administration (8.0%) and one after subcutaneous administration (4.3%). The v-safe call center attempted to contact 16 participants who reported a medically attended health event; six were contacted and two completed a VAERS report (both reported clinic visits for rash).

## DISCUSSION

JYNNEOS post-licensure and post-authorization vaccine safety surveillance findings for adults from VAERS and v-safe are generally consistent with the pre-licensure clinical trial findings. Serious AEs were rare. Causes of death in the four deaths reported to VAERS do not indicate any link with mpox vaccination. VAERS and v-safe did not identify any unexpected safety concerns for JYNNEOS. Syncope and anaphylaxis are both AEs that can occur with any injectable vaccine, therefore it was expected that some cases of each would be reported to VAERS for JYNNEOS. The syncope and anaphylaxis reporting rates for JYNNEOS are similar to rates previously reported for other types of vaccines.[14,15]

Intradermal administration of JYNNEOS was authorized as an emergency measure during this outbreak. Intradermal injection is not currently used for any routinely recommended vaccines in the United States. Vaccine administration errors were reported at a higher rate for intradermal compared to subcutaneous injection, which might be due to providers having less experience with intradermal injection or because the technique is more difficult. Overall, adverse health events were reported to VAERS at similar rates for intradermal and subcutaneous injection. There were minor differences in the types of AEs reported for each route of administration. Syncope was reported about four times more often with intradermal injection compared to subcutaneous. Also, intradermal injection may be more likely to cause injection site scarring or skin discoloration.

The VAERS reporting rates for myocarditis (8.64 cases per million doses) and pericarditis (5.38 cases per million doses) within 30 days after JYNNEOS were similar to previously published population background rates for these conditions and were substantially lower than with older smallpox vaccines. The rate of myocarditis after live, replicating smallpox vaccines in observational cohort studies ranged from 78 to 5,230 cases per million doses.[16,17] Population background rates (converted to a 30 day period) of myocarditis were 21.6 cases per million people in a U.S. military cohort, 2.4 in Ontario, Canada, and ranged from 2.7 to 7.5 among adult males in the MarketScan database; and for pericarditis were 22.8 in Italy and 4.7 for hospitalized cases in the United States.[8,16,18–20] VAERS reporting rates for myocarditis or pericarditis following JYNNEOS vaccination do not suggest an increased risk above background rates, but the possibility of a small risk cannot be excluded because: 1) cases occurring after vaccination might be underreported to VAERS, although serious AEs are more likely to be reported than non-serious AEs; 2) published population background rates might not accurately represent the expected rate in the JYNNEOS vaccinated cohort due to different distribution of risk factors in the population. Several case reports from the 2022 mpox outbreak have implicated monkeypox virus infection as a possible cause of myocarditis,[21] therefore any potential risk of myocarditis after JYNNEOS should be weighed against the potential benefit of JYNNEOS to prevent myocarditis due to monkeypox virus infection.

These two vaccine safety surveillance systems have different strengths and weaknesses. VAERS is an ongoing system used for all vaccines that is well suited to rapidly detect rare and serious AEs. The adverse health events most commonly reported to VAERS for JYNNEOS were injection site reactions. These types of non-serious events are typically under-reported due to the passive nature of VAERS, so the reporting rates do not represent the true rate at which these non-serious reactions occur. V-safe for mpox was set up in response to the mpox public health emergency as a temporary system. V-safe relied on individuals to enroll themselves as participants, but once enrolled, participants were actively reminded to complete surveys. V-safe AE rates are calculated from completed survey responses and are thus more accurate for common non-serious reactions compared to VAERS. The frequencies of local and systemic reactions reported to v-safe after JYNNEOS were similar to those reported in clinical trials.[3,22] V-safe was not well suited to collect information about rare AEs. V-safe enrollment was low in absolute numbers and as a percentage of national vaccine recipients; v-safe captured information for about 0.24% of doses administered during the period v-safe was open for enrollment. The v-safe cohort might not be representative of all vaccinees because participants were self-selected and not a random sample. V-safe attempted to facilitate VAERS reporting from people who reported medically attended health impact events, and two VAERS reports were obtained from this follow-up.

VAERS reporting rates were calculated using national vaccine administration data collected in response to the mpox public health emergency. Vaccine administration data did not include information about coadministration of other vaccines on the same day as JYNNEOS, so few conclusions can be drawn about the safety of simultaneous administration. VAERS reporting rates for women were about two times greater compared to men; sex differences in

AE rates have been observed previously for other vaccines, but it remains unclear if there is a true difference or if women are more likely to report AEs.[23,24]

There is currently limited data about the safety of JYNNEOS vaccination in children and pregnant women. Relatively few individuals aged <18 years received JYNNEOS vaccine during this U.S outbreak and few adverse health events were reported for this group. A clinical trial is underway in the United States to evaluate subcutaneous administration in adolescents aged 12 through 17 years.[25] CDC is not aware that any pregnant women received JYNNEOS during this outbreak and there were no VAERS or v-safe reports of vaccination during pregnancy.

These vaccine safety findings support the use of JYNNEOS for persons at risk of mpox as recommended by the Advisory Committee on Immunization Practices.[26] CDC and FDA will continue to monitor the safety of JYNNEOS. Healthcare providers and vaccine recipients should continue to report AEs after JYNNEOS to VAERS. The potential for a small risk of rare AEs, such as myocarditis, might only be detected after larger numbers of people receive the vaccine.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments:

CDC Mpox Emergency Response Data, Analytics, and Visualization Task Force.

### Conflict of Interest and Sources of Funding:

None declared.

## REFERENCES

1. McQuiston JH, Braden CR, Bowen MD, et al. The CDC Domestic Mpox Response - United States, 2022–2023. MMWR Morb Mortal Wkly Rep. May 19 2023;72(20):547–552. [PubMed: 37200231]
2. CDC. Interim clinical considerations for use of JYNNEOS and ACAM2000 vaccines during the 2022 U.S. monkeypox outbreak. US Department of Health and Human Services, CDC. Updated March 22, 2023. https://www.cdc.gov/poxvirus/monkeypox/clinicians/vaccines/vaccine-considerations.html
3. FDA. JYNNEOS [package insert, revised June 2021]. US Department of Health and Human Services, Food and Drug Administration. https://www.fda.gov/media/131078/download
4. FDA. Emergency use authorization for the emergency use of JYNNEOS. US Department of Health and Human Services, Food and Drug Administration. https://www.fda.gov/media/160774/download
5. Rao AK, Petersen BW, Whitehill F, et al. Use of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating) for Preexposure Vaccination of Persons at Risk for Occupational Exposure to Orthopoxviruses: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. Jun 3 2022;71(22):734–742. [PubMed: 35653347]
6. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. Aug 26 2015;33(36):4398–405. [PubMed: 26209838]
7. CIOMS. Glossary of ICH terms and definitions. 2023. 20 July 2023

8. Oster ME, Shay DK, Su JR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. JAMA. Jan 25 2022;327(4):331–340. [PubMed: 35076665]
9. Gold MS, Amarasinghe A, Greenhawt M, et al. Anaphylaxis: Revision of the Brighton collaboration case definition. Vaccine. Apr 6 2023;41(15):2605–2614. [PubMed: 36435707]
10. Kriss JL, Boersma PM, Martin E, et al. Receipt of First and Second Doses of JYNNEOS Vaccine for Prevention of Monkeypox - United States, May 22-October 10, 2022. MMWR Morb Mortal Wkly Rep. Oct 28 2022;71(43):1374–1378. [PubMed: 36301741]
11. Myers TR, Marquez PL, Gee JM, et al. The v-safe after vaccination health checker: Active vaccine safety monitoring during CDC's COVID-19 pandemic response. Vaccine. Feb 10 2023;41(7):1310–1318. [PubMed: 36697313]
12. See e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.
13. Carrubba S, Geevarghese A, Solli E, et al. Novel severe oculocutaneous manifestations of human monkeypox virus infection and their historical analogues. Lancet Infect Dis. May 2023;23(5):e190–e197. [PubMed: 36702137]
14. Su JR, Moro PL, Ng CS,et al. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990–2016. J Allergy Clin Immunol. Apr 2019;143(4):1465–1473. [PubMed: 30654049]
15. Hause AM, Gee J, Johnson T, et al. Anxiety-Related Adverse Event Clusters After Janssen COVID-19 Vaccination - Five U.S. Mass Vaccination Sites, April 2021. MMWR Morb Mortal Wkly Rep. May 7 2021;70(18):685–688. [PubMed: 33956781]
16. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. JAMA. Jun 25 2003;289(24):3283–9. [PubMed: 12824210]
17. Mandra AM, Superior MJ, Guagliardo SAJ, et al. Myopericarditis Associated With Smallpox Vaccination Among US Army Personnel - Fort Hood, Texas, 2018. Disaster Med Public Health Prep. Jun 2022;16(3):1022–1028. [PubMed: 33719991]
18. Nasreen S, Calzavara A, Buchan SA, et al. Background incidence rates of adverse events of special interest related to COVID-19 vaccines in Ontario, Canada, 2015 to 2020, to inform COVID-19 vaccine safety surveillance. Vaccine. May 26 2022;40(24):3305–3312. [PubMed: 35527057]
19. Imazio M, Cecchi E, Demichelis B, et al. Myopericarditis versus viral or idiopathic acute pericarditis. Heart. Apr 2008;94(4):498–501. [PubMed: 17575329]
20. Kumar N, Pandey A, Jain P, Garg N. Acute Pericarditis-Associated Hospitalization in the USA: A Nationwide Analysis, 2003–2012. Cardiology. 2016;135(1):27–35. [PubMed: 27164938]
21. Jaiswal V, Sultana Q, Lahori S, et al. Monkeypox-Induced Myocarditis: A Systematic Review. Curr Probl Cardiol. May 2023;48(5):101611. [PubMed: 36716982]
22. Frey SE, Wald A, Edupuganti S, et al. Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naive subjects. Vaccine. Sep 22 2015;33(39):5225–34. [PubMed: 26143613]
23. Cook IF. Sex differences in injection site reactions with human vaccines. Hum Vaccin. Jul 2009;5(7):441–9. [PubMed: 19377279]
24. Harris T, Nair J, Fediurek J, Deeks SL. Assessment of sex-specific differences in adverse events following immunization reporting in Ontario, 2012–15. Vaccine. May 2 2017;35(19):2600–2604. [PubMed: 28365252]
25. NIAID. A Phase 2 Randomized Multisite Trial to Inform Public Health Strategies Involving the Use of MVA-BN Vaccine for Mpox. National Library of Medicine. Updated August 1, 2023. https://clinicaltrials.gov/study/NCT05740982
26. CDC. ACIP Recommendations. https://www.cdc.gov/vaccines/acip/recommendations.html

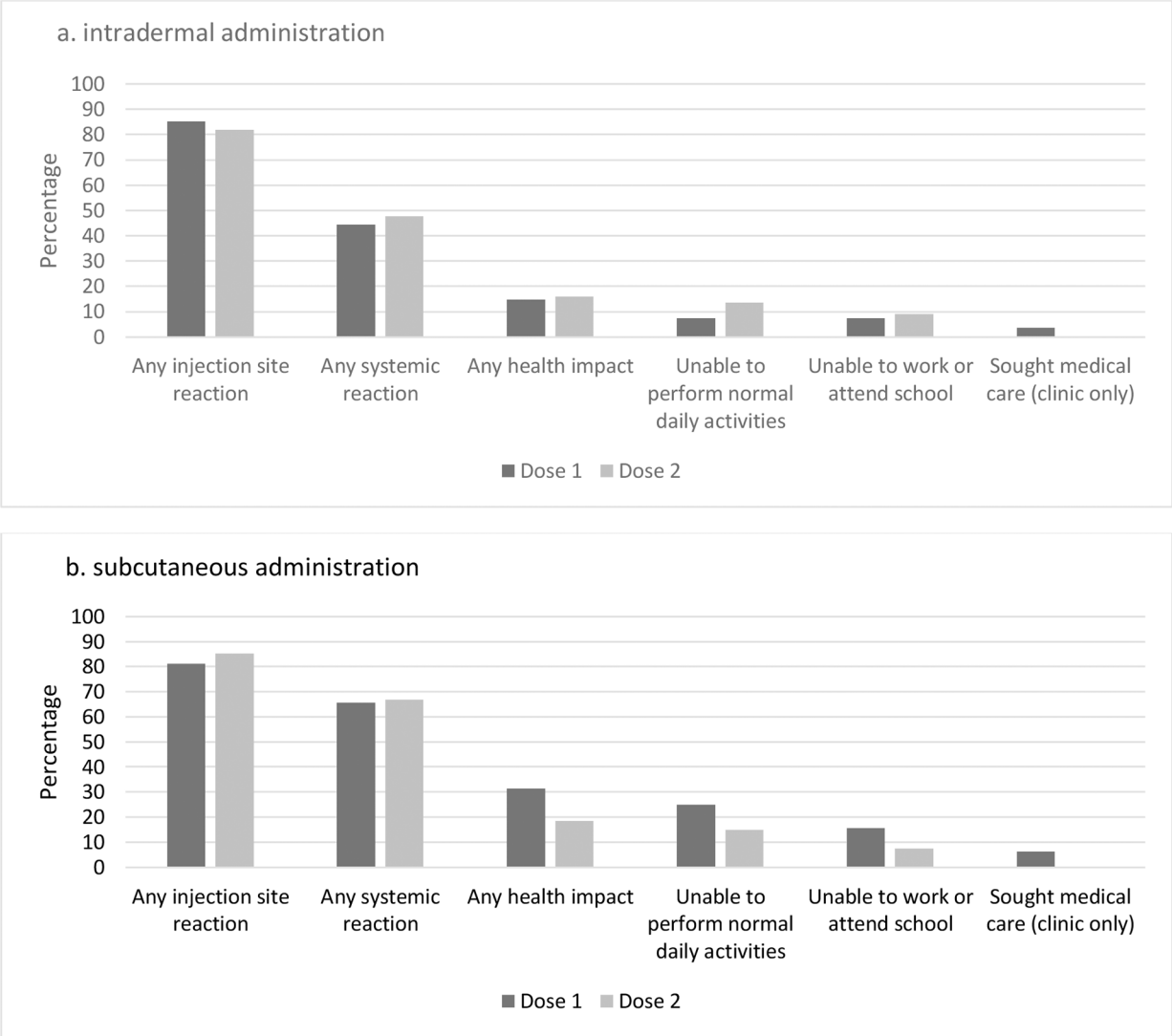


**Figure 1.**

V-safe, percentage of participants who reported injection site and systemic reactions and health impacts at least once in the first week after vaccination, by route of administration, November 16, 2022 – March 21, 2023.

**Table 1.**

Vaccine Adverse Event Reporting System (VAERS), characteristics of reports that include JYNNEOS vaccine, May 22, 2022 through March 31, 2023

| Characteristic | VAERS reports, n (%) N = 1,927 | Doses administered, n (%) N= 1,207,056 | Reporting rate per million doses |
|---|---|---|---|
| Sex | | | |
| Male | 1494 (77) | 1,096,178 (91) | 1,363 |
| Female | 249 (13) | 92,397 (8) | 2,695 |
| Not reported | 184 (10) | 18,481 (1) | 9,956 |
| Age group, years | | | |
| 0–11 | 0 (0) | 941 (<1) | 0 |
| 12–17 | 25 (1) | 824 (<1) | 30,340 |
| 18–49 | 1253 (65) | 852,054 (71) | 1,471 |
| 50–64 | 319 (17) | 276,830 (23) | 1,152 |
| ≥65 | 89 (5) | 76,396 (6) | 1,165 |
| Not reported | 241 (12) | 11 (<1) | n/a |
| Dose in series | | | |
| First | 1042 (54) | 744,075 (62) | 1,400 |
| Second | 556 (29) | 462,981 (38) | 1,201 |
| Not reported or other | 329 (17) | n/a | n/a |
| Route of administration | | | |
| Intradermal | 1107 (57) | 645,870 (54) | 1,714 |
| Subcutaneous | 380 (20) | 372,310 (31) | 1,021 |
| Intramuscular * | 174 (9) | 30,571 (2) | 5,692 |
| Not reported or other | 266 (14) | 158,305 (13) | 1,680 |
| Other vaccines administered on the same day as JYNNEOS † | | | |
| None | 1844 (96) | n/a | n/a |
| COVID-19 monovalent | 32 (2) | n/a | n/a |
| COVID-19 bivalent | 27 (1) | n/a | n/a |
| Influenza | 16 (1) | n/a | n/a |
| Others | 17 (1) | n/a | n/a |
| Seriousness classification ‡ | | | |
| Nonserious | 1893 (98) | n/a | 1,568 ¶ |
| Serious | 34 (2) | n/a | 28 ¶ |
| Adverse event categories † | | | |
| JYNNEOS vaccine administration error | 959 (50) | n/a | 794 ¶ |
| Adverse health event | 921 (48) | n/a | 763 ¶ |
| Reporter (primary report) | | | |

| Characteristic | VAERS reports, n (%) N = 1,927 | Doses administered, n (%) N= 1,207,056 | Reporting rate per million doses |
|---|---|---|---|
| Manufacturer | 296 (15) | n/a | n/a |
| Other | 120 (6) | n/a | n/a |
| Parent/guardian/caregiver | 1 (0) | n/a | n/a |
| Provider | 1175 (61) | n/a | n/a |
| Patient | 335 (17) | n/a | n/a |

n/a, not applicable.

[*] JYNNEOS is neither approved nor authorized for administration by intramuscular injection.

[†] Categories are not mutually exclusive.

[‡] Based on the U. S. Code of Federal Regulations (21 CFR 600.80), classification of a serious adverse event includes a report of one of the following: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly, or birth defect.

[¶] The reporting rates for these categories were calculated using the total number of doses administered as the denominator.

**Table 2.**

Vaccine Adverse Event Reporting System (VAERS) vaccine administration error and adverse health event reporting rates per million doses by route of JYNNEOS administration.

| | | All reports | | Vaccine administration error | | Adverse health event | |
|---|---|---|---|---|---|---|---|
| **Route of administration** | **Doses administered** | **VAERS reports** | **Reporting rate per million doses** | **VAERS reports** | **Reporting rate per million doses** | **VAERS reports** | **Reporting rate per million doses** |
| Subcutaneous | 372,310 | 380 | 1,021 | 118 | 317 | 251 | 674 |
| Intradermal | 645,870 | 1,107 | 1,714 | 628 | 972 | 444 | 687 |
| Intramuscular | 30,571 | 174 | 5,692 | 155 | 5,070 | 21 | 687 |
| Not reported or other | 158,305 | 266 | 1,680 | 58 | 366 | 205 | 1,295 |

**Table 3.**

Vaccine Adverse Event Reporting System (VAERS), adverse health events reported after JYNNEOS vaccination by route of administration*

| Subcutaneous | | | Intradermal | | |
|---|---|---|---|---|---|
| **Event** | **n** | **Rate†** | **Event** | **n** | **Rate†** |
| Injection site erythema | 42 | 113 | Injection site erythema | 97 | 150 |
| Injection site swelling | 42 | 113 | Dizziness | 81 | 125 |
| Injection site pain | 39 | 105 | Injection site swelling | 72 | 111 |
| Pain | 38 | 102 | Urticaria | 70 | 108 |
| Erythema | 31 | 83 | Injection site pruritus | 58 | 90 |
| Fatigue | 29 | 78 | Erythema | 50 | 77 |
| Dizziness | 28 | 75 | Syncope | 47 | 73 |
| Headache | 27 | 73 | Pruritus | 46 | 71 |
| Pyrexia | 26 | 70 | Hyperhidrosis | 44 | 68 |
| Injection site pruritus | 25 | 67 | Loss of consciousness | 43 | 67 |
| Nausea | 22 | 59 | Injection site pain | 38 | 59 |
| Pruritus | 22 | 59 | Pallor | 32 | 50 |
| Rash | 22 | 59 | | | |
| Injection site induration | 20 | 54 | | | |

*Only licensed or authorized routes of administration are shown.

†Reporting rate per million doses administered. Only events with a reporting rate ≥50 are shown.

**Table 4.**

V-safe for mpox demographic characteristics of active participants, November 16, 2022 – March 21, 2023

| Characteristic | N=213 n (%) |
|---|---|
| Age in years | |
| 18–49 | 136 (63.8) |
| 50–64 | 64 (30.0) |
| ≥65 | 13 (6.1) |
| Sex | |
| Male | 174 (81.7) |
| Female | 36 (16.9) |
| Other or prefer not to answer | 3 (1.4) |
| Gender identity | |
| Male | 166 (77.9) |
| Female | 31 (14.6) |
| Transgender | 9 (4.2) |
| None of the above or prefer not to answer | 7 (3.3) |
| Race/Ethnicity | |
| Asian, non-Hispanic | 13 (6.1) |
| Black, non-Hispanic | 15 (7.0) |
| Multi-racial, non-Hispanic | 11 (5.2) |
| Other race, non-Hispanic | 3 (1.4) |
| White, non-Hispanic | 127 (59.6) |
| Hispanic | 35 (16.4) |
| Unknown race or ethnicity | 9 (4.2) |
| Pre-existing health Conditions | |
| Atopic dermatitis, psoriasis, or eczema | 23 (10.8) |
| Eye disease treated with topical steroids | 1 (0.5) |
| Immunocompromised* | 35 (16.4) |
| Heart problems | 14 (6.6) |
| Pregnant | 0 (0) |
| Breastfeeding | 1 (0.5) |

* Immunocompromised was defined as self-report of immunocompromising condition or taking immunosuppressive medications at the time of vaccination.