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Thromboembolic events after Ad.26.COV2.S COVID-19 vaccine: Reports to the Vaccine Adverse Event Reporting System

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Abstract

Purpose: The Food and Drug Administration (FDA) has identified a potential safety concern for thromboembolic events (TEEs) after Ad.26.COV2.S COVID-19 Vaccine. We sought to characterize the frequency, severity, type, and anatomic location of TEEs reported to the Vaccine Adverse Event Reporting System (VAERS) following Ad.26.COV2.S.

Methods: Reports of TEEs after Ad.26.COV2.S were identified in VAERS, and demographics, clinical characteristics, and relevant medical history were summarized. For a subset of reports, physicians reviewed available medical records and evaluated clinical presentation, diagnostic evaluation, risk factors, and treatment. The crude reporting rate of TEEs was estimated based on case counts in VAERS and vaccine administration data.

Results: Through February 28, 2022, FDA identified 3790 reports of TEEs after Ad.26.COV2.S. Median age was 56 years, and 1938 individuals (51.1%) were female. Most reports, 2892 (76.3%), were serious, including 421 deaths. Median time to onset was 12 days post-vaccination. Obesity and ischemia were among the most commonly documented risk factors. Thrombocytopenia (platelet count less than 150 000/μl) was documented in 63 records (11.5%) and anti-platelet 4 antibodies in 25 (4.6%). Medical review identified cases of severe clot burden (e.g., bilateral, saddle, or other massive pulmonary embolism with or without cor pulmonale; lower extremity thrombus involving the external iliac, common femoral, popliteal, posterior tibial, peroneal, and gastrocnemius veins). The crude reporting rate was ~20.7 cases of TEE per 100 000 doses of Ad.26.COV2.S administered.

Conclusions: Life-threatening or fatal TEEs have been reported after Ad.26.COV2.S, including bilateral massive pulmonary embolism or other severe clot burden.

KEYWORDS

Ad.26.COV2.S COVID-19 vaccine, coagulopathy, coronavirus, embolism, SARS-CoV2, thrombus, VAERS

Key points

- The Vaccine Adverse Event Reporting System has received 3790 reports of thromboembolic events (TEEs), with or without thrombocytopenia, in individuals who received Ad.26.COV2.S COVID-19 Vaccine.
- Median time to onset was 12 days, and the majority of TEEs were serious, including 421 deaths.
- The most striking cases of TEE included severe clot burden (e.g., saddle pulmonary embolism with or without cor pulmonale; lower extremity thrombus involving the external iliac, common femoral, popliteal, posterior tibial, peroneal, and gastrocnemius veins).
- Obesity and ischemia were among the most commonly documented risk factors.
- Further research may elucidate the pathophysiological mechanism of hypercoagulability following Ad26.COV2.S vaccination.

Plain language summary

As part of routine public health activities, the Food and Drug Administration reviews side effects that have been reported to the Vaccine Adverse Event Reporting System (VAERS). From February 27, 2021 to February 28, 2022, VAERS received 3790 reports of blood clots in people who had received Janssen COVID-19 Vaccine. Most cases were serious (e.g., life-threatening, fatal, or required hospitalization). Some of the clots were very severe (e.g., extending from the ankle to the groin, or involving both lungs at the same time). Some people had abnormal levels of platelets (blood cells that help the body stop bleeding), but many did not. Reports in VAERS do not prove that a vaccine caused an adverse event. More research is needed to understand whether Janssen COVID-19 Vaccine can cause blood clots.

1 | INTRODUCTION

On February 27, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Janssen COVID-19 Vaccine,[1] followed by interim recommendations by the Advisory Committee on Immunization Practices (ACIP).[2] Ad.26.COV2.S uses a replication-incompetent human adenoviral type 26 vector platform and is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.[1,3] The FDA's EUA review focused on a randomized, double-blind, placebo-controlled trial; safety was assessed in 21 895 vaccine recipients and 21 888 individuals who received placebo.[4]

Post-authorization safety surveillance in the Vaccine Adverse Event Reporting System (VAERS) identified reports of thrombosis with thrombocytopenia syndrome (TTS), also known as vaccine-induced immune thrombotic thrombocytopenia (VITT), after Ad.26.COV2.S.[5,6] On April 13, 2021, the FDA and Centers for Disease Control and Prevention (CDC) recommended a pause in the use of this vaccine out of an abundance of caution.[7] Upon review by the FDA, CDC, and ACIP, the pause was lifted on April 23, 2021[8] and the product Fact Sheets was updated to include a Warning about TTS.[3]

As part of continual, routine safety surveillance, FDA has also identified VAERS reports of thromboembolic events (TEEs), with or without thrombocytopenia, following Ad.26.COV2.S. The objective of this review is to summarize the frequency, severity, type, and anatomic location of TEEs reported after Ad.26.COV2.S vaccination.

2 | METHODS

VAERS is a national passive surveillance system for monitoring vaccine safety.[9,10] Established in 1990, VAERS is jointly managed by the U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention. Reports are submitted by clinicians, vaccine recipients or their parents or guardians, vaccine manufacturers, and other interested parties. Before the COVID-19 pandemic, VAERS in recent years had received more than 50 000 reports per year. In 2021, VAERS received 1 063 298 reports. FDA physicians review reports of serious events, defined as events that are fatal, disabling, or life-threatening; require or prolong hospitalization; result in congenital anomalies; require medical intervention to prevent such outcomes; or are deemed to be other medically important conditions.[11] An FDA physician has manually reviewed all serious direct reports (i.e., reports from patients, healthcare providers, health departments, and other non-manufacturer parties) for Ad.26.COV2.S since the vaccine was authorized.

We performed two assessments of VAERS reports of TEE following Ad.26.COV2.S: an overview of all TEE reports and an intensive review of a selected subset. For the first assessment ("overview"), we employed two complementary methods: daily review of serious reports by an FDA physician, and automated query of VAERS for

Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Queries (SMQs): Embolic and thrombotic events, arterial (SMQ); Embolic and thrombotic events, venous (SMQ); and Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ). For the VAERS database automated query, we included all US VAERS reports (regardless of seriousness or age) for individuals vaccinated with Ad.26.COV2.S between February 27, 2021, and February 28, 2022 (inclusive).

After TTS was identified as a safety concern, a team of FDA physicians conducted an additional assessment ("intensive review"). We identified reports based on the three aforementioned SMQs, but we limited the review to serious[11] US reports of TEE in individuals 18 to 64 years of age, received February 27, 2021 through May 25, 2021. We omitted individuals 65 years of age and older, because the background risks of venous[12] and arterial cardiovascular events[13] increase with age, and we felt that focusing on a group with a lower baseline risk was important at this stage of evaluating a possible association of TEE and Ad.26.COV2.S vaccination. Initial and follow-up reports, medical records, and any other available documents were reviewed to ascertain the clinical presentation, diagnostic evaluation, risk factors, and treatment of each case. The following were assessed and summarized: patient demographics, onset time to the earliest sign or symptom of a clotting event, category of thrombosis/embolism (i.e., venous, arterial, mixed, or unknown), anatomic location of thrombi/emboli, confirmatory studies (e.g., computerized tomography, ultrasound, or magnetic resonance imaging), laboratory values (including changes or trends over time, for any given patient), treatment (including heparin exposure after the onset of thrombosis), concomitant exposures, risk factors, medical history, reported outcome, and any additional information deemed salient, based on medical judgment (Appendix). Pertinent positives (e.g., personal history of deep vein thrombosis, family history of factor V Leiden mutation) and negatives (e.g., anti-platelet 4 [PF4] antibodies absent, no recent travel) were recorded and descriptively analyzed.

The crude reporting rate of TEEs was estimated based on report counts in VAERS ("overview") and vaccine administration data. As part of routine safety surveillance, FDA applied Empirical Bayesian (EB) data mining[14] to identify MedDRA PTs that were disproportionally reported (i.e., reported more frequently than expected compared with other vaccines in VAERS) after the administration of Ad.26.COV2.S, adjusting for age, sex, and year of reporting. The EB method computes signal scores for vaccine-PT pairs compared to other vaccine-PT pairs (i.e., the comparator includes all other vaccines and all other PTs within VAERS).[14] We applied a published criterion of EB05 ≥2.0, where EB05 represents the lower bound of the 90% confidence interval surrounding the EB geometric mean.[15] An EB05 ≥2.0 indicates that a particular vaccine-event pair occurs at least twice as often as expected than by chance alone. An elevated EB05 value does not imply a causal relationship but can be used as a threshold for further assessment of an event. The work was completed as part of routine safety surveillance by the FDA. No interventional treatments, exposures, or procedures were performed; therefore, this work was not subject to Institutional Review Board evaluation and informed consent requirements.

3 | RESULTS

3.1 | Overview

Through February 28, 2022, FDA identified 3790 reports (serious and non-serious[11]) of TEEs after Ad.26.COV2.S (Table 1). The median age was 56 years (interquartile range 44–66), and 1938 individuals (51.1%) were female. The median time to onset, as reported on the VAERS form, was 12 days post-vaccination (interquartile range 3–28). The majority of cases, 2892 (76.3%), were serious, including 421 deaths.

More than half of reports (1968; 51.9%) stated that the patient had not recovered. Twelve reports (0.3%) listed concomitant vaccines (data not shown). The Table lists the most common post-vaccination Preferred Terms (PTs) that is, clinical terms reported in association with TEE. Notably, some terms are not adverse events, but pertain to radiographic evaluations or treatment related to coagulopathic events. The table also lists the most frequent pre-vaccination PTs, i.e., past medical history, as reported on the VAERS form. Almost half of TEE reports (1676; 44.2%) listed no previous medical conditions. Among reports that listed pre-existing conditions, the most common were hypertension, hyperlipidaemia, obesity, and diabetes mellitus. MedDRA Preferred Terms (PTs) are not medically confirmed diagnoses.

3.2 | Intensive review

After consolidation of duplicates and removal of reports with insufficient information, the search strategy identified 546 serious[11] US reports of TEE in individuals 18–64 years of age from February 27, 2021 through May 25, 2021. The median patient age was 51 years (interquartile range 41–59), and 310 individuals (57%) were female. Median time to onset of the first sign or symptom of TEE was 9 days post-vaccination (interquartile range 4–17). A minority of patients (97; 17.8%) reportedly recovered, but nearly half (271; 49.6%) did not. For the remaining cases (178; 32.6%), the recovery status was unknown.

Venous thromboses were the most common TEE (288; 52.7%), followed by arterial (178; 32.6%), mixed (37; 6.8%), and unspecified (43; 7.9%). The most common clinical manifestations included pulmonary embolism (PE) (195; 35.7%), deep venous thrombosis (DVT) (141; 25.8%), cerebrovascular accident (131; 24.0%), and myocardial infarction (54; 9.9%) (not mutually exclusive). Almost one-third of people (169; 31%) experienced clots in multiple places (e.g., bilateral DVTs and bilateral PE; myocardial infarction and pulmonary embolism). Management of clots included anticoagulants, thrombolytics, thrombectomy, and amputation. Of note, our search results also included reports of TTS, including cerebral venous sinus thrombosis, which have previously been described.[5,6]

Radiographic and laboratory investigations varied. Three hundred ninety-nine cases (73.1%) included at least one confirmatory study, such as computerized tomogram angiography (CTA) (247; 45.2%), ultrasound (104; 19.0%), or magnetic resonance angiography or

TABLE 1 Demographics of patients and characteristics of thromboembolic events after Ad.26.COV2.S vaccine (VAERS overview February 27, 2021–February 28, 2022)

Age[a] (years)	
n	3157
Mean (standard deviation)	55.3 (16.3)
Median (interquartile range)	56 (44–66)
Sex	
Female	1938 (51.1%)
Male	1646 (43.4%)
Not reported	206 (5.4%)
Race	
White	1966 (51.9%)
Black	305 (8.0%)
Mixed race	101 (2.7%)
Other race	93 (2.5%)
Not reported	1325 (35.0%)
Ethnicity	
Non-Hispanic	1910 (50.4%)
Hispanic	222 (5.9%)
Not reported	1658 (43.7%)
Time to onset[b] (days)	
n	3043
Mean (standard deviation)	29.7 (51.0)
Median (interquartile range)	12 (3–28)
Seriousness[c] and reported outcomes	
Serious	2892 (76.3%)
Hospitalized	1965 (51.9%)
Life-threatening	841 (22.2%)
Died	421 (11.1%)
Permanent disability	398 (10.5%)
Hospitalization prolonged	21 (0.6%)
Congenital anomaly	7 (0.2%)
Recovered[d]	
No	1968 (51.9%)
Unknown	1124 (29.7%)
Yes	698 (18.4%)
Pregnant	20 (0.8%)
Most frequent post-vaccination preferred terms[e]	
Thrombosis	1215 (32.1%)
Pulmonary embolism	777 (20.5%)
Deep vein thrombosis	695 (18.3%)
Dyspnoea	667 (17.6%)
Anticoagulant therapy	646 (17.0%)
Headache	627 (16.5%)
Pain in extremity	623 (16.4%)
Cerebrovascular accident	602 (15.9%)
Ultrasound Doppler abnormal	408 (10.8%)
Chest pain	399 (10.5%)

TABLE 1 (Continued)

Age[a] (years)	
Most frequent pre-vaccination preferred terms[e]	
No previous medical conditions reported	1676 (44.2%)
Hypertension	913 (24.1%)
Hyperlipidaemia	349 (9.2%)
Obesity	294 (7.8%)
Diabetes mellitus	272 (7.2%)
Gastrooesophageal reflux disease	251 (6.6%)
Depression	231 (6.1%)
Type 2 diabetes mellitus	223 (5.9%)
Asthma	211 (5.6%)
Anxiety	186 (4.9%)

[a]For 633 reports, age was missing.
[b]Time to symptom onset, as reported on the VAERS form. For 747 values, onset time was missing.
[c]Serious: events that are reported as resulting in death, life-threatening adverse experience, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect.[11] These designations are defined by the reporter's input. Serious criteria are not mutually exclusive.
[d]Recovery status is defined by the reporter's input (yes, no, unknown) at the time of reporting and may not reflect whether the patient later died or became permanently disabled.
[e]Preferred Terms are not medically confirmed diagnoses, and they are not mutually exclusive.

venography (63; 11.5%); studies are not mutually exclusive. Thrombocytopenia (platelet count less than 150 000/μl) was documented in 63 records (11.5%) and PF4 antibodies in 25 (4.6%). The small number of available values for fibrinogen nadir and peak D-dimer precluded meaningful analysis.

Available information about risk factors varied in both quantity and quality. Pre-existing risk factors for ischemia (e.g., coronary artery disease, hypertension, diabetes, or hyperlipidemia) were documented in 198 records (36.3%), while 110 records (20.1%) explicitly stated that the patient had none; the remaining records provided no information about this risk factor. Similarly, 78 records (14.3%) mentioned obesity, 70 (12.8%) confirmed its absence, and the rest contained no comments about obesity. For other risk factors, reporting was low: oral contraceptives or menopausal hormone therapy (47 cases), malignancy (25), a long flight or other trip (17), recent surgery (14), hereditary thrombophilia (12), acquired thrombophilia (6), and pregnancy (6). Four people had received heparin in the 100 days preceding thrombosis, and 67 received it after the onset of clot signs or symptoms. A minority of records contained information about preceding COVID-19 disease: 126 cases (23.1%) included documentation regarding infection within the month preceding thrombosis (14 yes and 112 no), and 62 records (11.4%) indicated whether the patient had ever tested positive for SARS-CoV2 (24 yes and 38 no).

In both the overview and the intensive review, medical review identified a number of severe TEE, including cases involving bilateral, saddle, or other massive pulmonary embolism with or without cor

pulmonale (e.g., saddle embolism with extensive involvement of pulmonary artery branches in all lobes, pulmonary emboli in main left and right pulmonary arteries), right ventricular thrombus, or other severe clot burden (e.g., upper extremity thrombus involving internal jugular, subclavian, axial and brachial veins; lower extremity thrombus involving the external iliac, common femoral, femoral, popliteal, posterior tibial, peroneal vein, and gastrocnemius veins). Thrombi occurred both with and without thrombocytopenia. Medical management was as described above.

3.3 | Reporting rate and data mining

From the date of EUA[1] through February 28, 2022, approximately 18 349 015 doses of Ad.26.COV2.S were administered to adults in the US.[16] The crude reporting rate was approximately 20.7 cases of TEE per 100 000 doses of Ad.26.COV2.S administered.

Empirical Bayesian data mining for Janssen COVID-19 Vaccine revealed disproportional reporting[14,15] for several relevant PTs. For clinical manifestations of TEE, data mining revealed elevated values for: Cerebral thrombosis, Cerebral venous sinus thrombosis, Deep vein thrombosis, Jugular vein thrombosis, Peripheral embolism, Pulmonary embolism, Pulmonary thrombosis, Superficial vein thrombosis, Thrombectomy, Thrombocytopenia, Thrombosis, Thrombosis with thrombocytopenia syndrome, and Transverse sinus thrombosis. In addition, values were elevated for the following laboratory and radiographic tests related to the evaluation of TEEs: Activated partial thromboplastin time prolonged, Activated partial thromboplastin time shortened, Angiogram cerebral abnormal, Angiogram pulmonary abnormal, Blood fibrinogen decreased, Computerized tomogram head abnormal, Computerized tomogram thorax abnormal, Fibrin D dimer increased, Heparin-induced thrombocytopenia test positive, Magnetic resonance imaging head abnormal, Mean cell hemoglobin concentration decreased, Ultrasound Doppler abnormal, and Venogram abnormal. The elevated values indicate that these clinical and laboratory terms were reported at least twice as frequently after Ad.26.COV2.S as would be expected, compared to other vaccines and other PTs.

4 | DISCUSSION

To improve our understanding of TEEs, with or without thrombocytopenia, we reviewed and summarized TEEs reported to VAERS following Ad.26.COV2.S vaccination. During this first year after authorization, 18 439 105 doses of Ad.26.COV2.S were administered.[16] Based on cases identified in VAERS through standardized queries, the observation of 3790 cases yields an overall crude reporting rate of approximately 20.7 cases of TEE per 100 000 doses of Ad.26.COV2.S administered. Given the methodology of our analysis, which included both arterial and venous events, and the limitations of passive surveillance in general, it is not possible to estimate a risk. However, for context, the annual incidence of venous thromboembolism is approximately 1–2 per 1000 (or 100–200 per 100 000).[12,17]

The findings were at times notable for severe clot burden (including clots in multiple sites) and clots in unusual locations. TTS[5,6] and immune thrombocytopenia[18] following Ad.26.COV2.S vaccination have previously been described. The Fact Sheet for the vaccine has been updated to include a Warning about TTS,[3] and immune thrombocytopenia is listed under Post Authorization Experience.[3] A distinguishing feature of TTS is the occurrence of clots in "unusual sites," but the American Society of Hematology (ASH) also states that the condition can involve "any venous or arterial thrombosis (often cerebral or abdominal)".[19]

Because of the morbidity and mortality associated with TEEs, including saddle embolus and other severe clot burden, we believe that these findings are important. It is unclear whether the safety concern for TEEs following receipt of Ad.26.COV2.S extends beyond TTS/VITT. Although some notable TEE cases met diagnostic criteria for TTS/VITT (clinical features plus low platelet count ± confirmatory PF4 antibody), other cases did not meet such criteria and diagnostic information was missing for a majority of cases.

It is not yet known whether TTS is completely distinct from TEEs that occur in "common" sites or striking cases of TEE that do not meet diagnostic criteria for TTS/VITT, or whether there is a spectrum of hypercoagulability following Ad26.COV2.S vaccination with a common underlying pathophysiological mechanism. Additional studies, including large-scale population studies leveraging electronic healthcare record data and mechanistic studies, are needed to answer this question. However, such studies may be unfeasible due to the low uptake of Ad.26.COV2.S in the US following the preferential recommendation of mRNA COVID-19 vaccines over Ad.26.COV2.S for primary and booster vaccination due to the risk of serious adverse events.[20]

Overall, the median time to symptom onset, as reported on the VAERS form, was 12 days after vaccination. However, within the subset selected for intensive review, the median onset time to the first sign or symptom of TEE was 9 days. The difference may be due to greater seriousness of cases in the subset and a lower percentage of missing values.

The overall study and the intensive review identified similar proportions of people who recovered (18.4% vs. 17.8%), who did not recover (51.9% vs. 49.6%), or whose status is not known (29.7% vs. 32.6%). This finding is somewhat surprising, since the overall study included all TEE cases and the subset included only serious reports.

The ASH web page about TTS/VITT[19] states: "Avoid use of heparin until VITT has been ruled out or until an alternative other plausible diagnosis has been made." The recommended work-up for VITT[19] includes PF4 antibody assays and other laboratory evaluations, but treatment might be initiated before test results are available. Due to small numbers in our review, we could not assess whether the use of heparin after TEE onset was affected by ASH's statement or by the pause in vaccine recommendations.[7]

This study has several limitations. In our review, even when hospital records were available, documentation about the present illness and past medical history varied considerably. Staffing shortages and severe strain on healthcare workers likely limited their ability to provide details; it was rare for reporters to state that a DVT was unprovoked and to enumerate pertinent negatives explicitly (e.g., "no recent

flights, no recent immobilization, no oral contraceptives"). In many cases, information about risk factors was not available and therefore such characteristics could not be evaluated. We must emphasize that "absence of proof" does not imply "proof of absence." For example, the absence of documentation of PF4 antibodies or factor V Leiden mutations does not imply that patients lacked these markers, but rather that the available records did not provide information about them. Similarly, only 14% of records stated that the patient was obese, but the prevalence of obesity in the US adult population is 42%.[21] This finding suggests that either the population in our review is highly skewed or that documentation of obesity (and likely other risk factors) was incomplete. Furthermore, data mining findings are subject to a number of limitations and do not imply causality; rather, they should be regarded as "hypothesis-generating".[14]

We limited the intensive review to serious[11] US reports in people 18–64 years of age within the first 3 months of vaccine availability under EUA. Because the background risks of venous[12] and arterial[13] events increase with age, including individuals 65 years and older might have obscured any potential signals. Future evaluations might include additional age groups and other subpopulations of varying background risk. In addition, few records indicated whether the patient had had recent COVID-19 infection or had ever had a positive test. Since COVID-19 is known to be associated with coagulopathy,[22–24] future analyses of TEEs should ideally include more complete information about recent or remote infection.

Strengths of VAERS include its national scope, size, timeliness, ability to detect events that were not observed during prelicensure trials, and surveillance among special populations.[9] Although the EUA[1] stipulates mandatory reporting requirements for the manufacturer and clinicians, passive surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, incomplete information, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups.[9,10] Because of these and other limitations, verifying causal associations between vaccines and adverse events, based on spontaneous reports alone, is usually not possible. Nevertheless, VAERS data are used to describe a range of potential vaccine adverse events and to look for unexpected patterns in demographics and clinical characteristics that might lead to hypotheses that can be tested with epidemiologic studies.[25] FDA and CDC are also conducting active surveillance with large scale population-based studies, using claims data or electronic healthcare record data. The population-based data sources include the FDA Biologics Effectiveness and Safety System,[26] the Center for Medicare and Medicaid Services databases,[27] and the CDC Vaccine Safety Datalink.[28]

5 | CONCLUSIONS

FDA has continually monitored the post authorization safety of COVID-19 vaccines through both active and passive surveillance, as well as review of safety data submitted by the manufacturers. The estimated crude rate of TEE following Ad.26.COV2.S. was not greater than the background rate of TEEs. Qualitatively, there were striking TEE cases marked by severe clot burden (including clots in multiple sites) and clots in unusual locations. It is unclear whether the safety concern for TEEs following receipt of Ad.26.COV2.S extends beyond TTS/VITT. Based on available safety information, the Fact Sheet for vaccination providers was revised to include "venous thromboembolism (with or without thrombocytopenia)" in Post Authorization Experience.[3] FDA will continue to monitor adverse events after all vaccines, including Ad.26.COV2.S.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

This work was conducted as part of routine vaccine safety activities and public health surveillance. No Institutional Review Board approval was required. Data are deidentified, and patient informed consent was not required.

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APPENDIX A

A.1 | Clinical data collected during intensive review of serious reports of TEE (February 27, 2021–May 25, 2021)

A.1.1. | Demographic characteristics and report data

- Age, sex, and race/ethnicity
- Onset time to the earliest sign or symptom of clotting event (e.g., headache, dyspnea, swelling, abdominal pain)
- Reported outcome

A.1.2. | Clot characteristics

- Clot types: venous, arterial, mixed, or unknown
- Anatomic location(s) of clot (not mutually exclusive): lower extremity/pelvis, pulmonary, coronary (myocardial infarction), central venous sinus, intraabdominal, cerebrovascular accident, or other

A.1.3. | Diagnostic evaluation

- Confirmatory studies performed: computerized tomography (CT), CT angiography, echocardiogram, sonogram, magnetic resonance (MR) imaging, MR angiography, etc.
- Laboratory evaluations: platelet count (including nadir), PF4 antibodies, fibrinogen (including nadir), D-dimer (including peak)

A.1.4. | Risk factors

- COVID-19: any history of COVID+ polymerase chain reaction, antigen, or other test
- COVID-19: COVID+ within 1 month prior to clotting event
- Heparin exposure after clot onset
- Heparin exposure within 100 days prior to clotting event
- History of ischemic/cardiovascular risk factor (coronary artery disease, hyperlipidemia, hypertension, diabetes mellitus, obesity)
- Immobilization or prolonged travel (>4 h) within 2 weeks prior to clotting event
- Malignancy
- Monoclonal antibodies
- Oral contraceptives or other hormonal treatment
- Pregnancy: current or within 6 weeks prior to clotting event
- Smoking
- Surgery or trauma within 3 months prior to clotting event
- Thrombophilia: hereditary or acquired
- Other