



# **Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine**

**Advisory Committee on Immunization Practices (ACIP)  
April 23, 2021**

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# Disclaimer

- The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC) or the U.S. Food and Drug Administration (FDA)
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC or FDA

# Topics

- Background
- Thrombosis with thrombocytopenia syndrome following Janssen COVID-19 vaccine
- Summary

**Background**

# Thrombosis\*

- Thrombosis occurs when blood clots block blood vessels
  - Thromboses can be venous or arterial
  - Complications include heart attack, stroke, infarctions
- Causes and risk factors include:
  - Trauma, immobility, inherited disorders (genetic), autoimmune disease, obesity, hormone therapy or birth control pills, pregnancy, smoking, cancer, older age, etc.
- Symptoms may include:
  - Pain and swelling in an extremity, chest pain, numbness or weakness on one side of the body, sudden change in mental status
- Diagnosed mainly through imaging (e.g., CT, MRI, ultrasound) and blood tests

# Platelets and thrombocytopenia (low platelets)\*

- Platelets (thrombocytes) are colorless blood cells that help blood clot; normal platelet count is 150,000–450,000 per microliter
- Platelets stop bleeding by clumping and forming plugs in blood vessel injuries
- Thrombocytopenia is a condition in which you have a low blood platelet count (<150,000 per microliter)
- Dangerous internal bleeding can occur when your platelet count falls below 10,000 platelets per microliter
- Though rare, severe thrombocytopenia can cause bleeding into the brain, which can be fatal

## AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets

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News 07/04/2021

### EMA confirms overall benefit-risk remains positive

EMA's safety committee (PRAC) has concluded today that unusual blood clots with low blood platelets should be listed as very rare side effects of Vaxzevria (formerly COVID-19 Vaccine AstraZeneca).

In reaching its conclusion, the committee took into consideration all currently available evidence, including the advice from an ad hoc expert group.

EMA is reminding healthcare professionals and people receiving the vaccine to remain aware of the possibility of very rare cases of blood clots combined with low levels of blood platelets occurring within 2 weeks of vaccination. So far, most of the cases reported have occurred in women under 60 years of age within 2 weeks of vaccination. Based on the currently available evidence, specific risk factors have not been confirmed.

People who have received the vaccine should seek medical assistance immediately if they develop symptoms of this combination of blood clots and low blood platelets (see below).

The PRAC noted that the blood clots occurred in veins in the brain (cerebral venous sinus thrombosis, CVST) and the abdomen (splanchnic vein thrombosis) and in arteries, together with low levels of blood platelets and sometimes bleeding.

The Committee carried out an in-depth review of 62 cases of cerebral venous sinus thrombosis and 24 cases of splanchnic vein thrombosis reported in the EU drug safety database (EudraVigilance) as of 22 March 2021, 18 of which were fatal.<sup>1</sup> The cases came mainly from spontaneous reporting systems of the EEA and the UK, where around 25 million people had received the vaccine.

COVID-19 is associated with a risk of hospitalisation and death. The reported combination of blood clots and low blood platelets is very rare, and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of side effects.

**Originally presented April 14, 2021**

National Center for Immunization & Respiratory Diseases



# **Reports of cerebral venous sinus thrombosis with thrombocytopenia after Janssen COVID-19 vaccine**

**Advisory Committee on Immunization Practices (ACIP)  
April 14, 2021**

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# Cerebral venous sinus anatomy

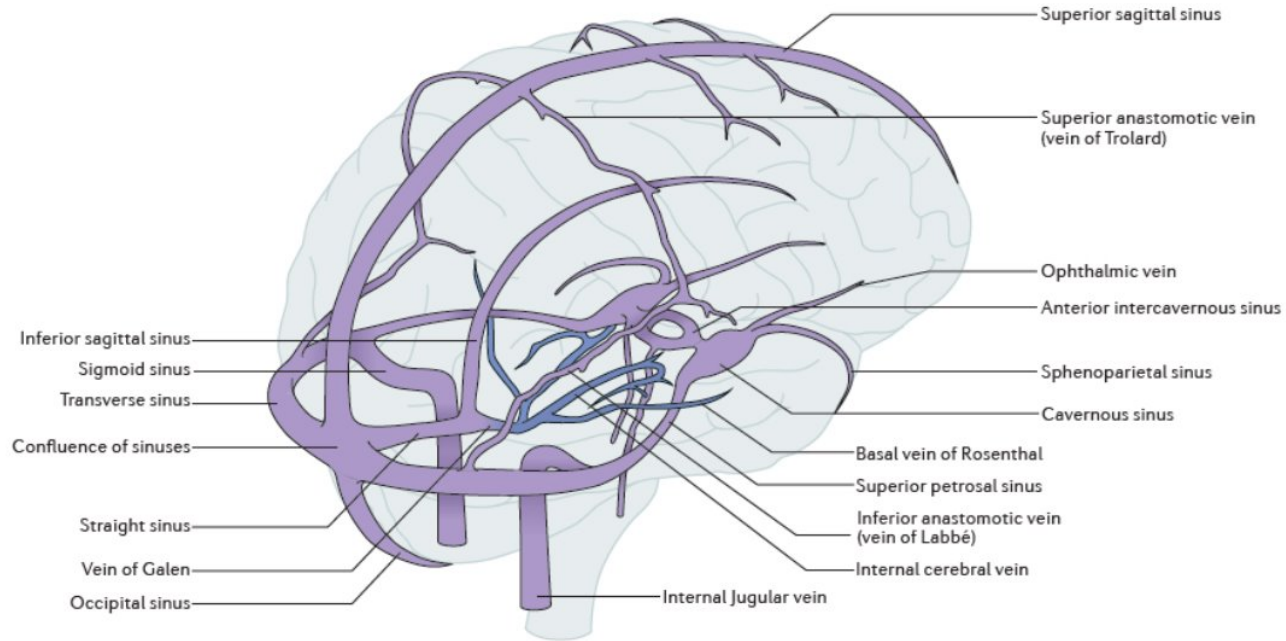


Figure 1 | **Anatomy of the cerebral venous system.** Diagram showing the main components of the cerebral venous system. Blue vessels represent the deep venous system.

# VAERS data for cerebral venous sinus thrombosis (CVST) reports following COVID-19 vaccines (ACIP April 14, 2021)

Originally presented April 14, 2021

## Reports of CVST to VAERS after COVID-19 vaccines as of April 12, 2021

- Janssen COVID-19 vaccine
  - 6 reports of CVST with thrombocytopenia (platelet counts  $<150\text{K}/\text{mm}^3$ ) following 6.86 million doses administered
    - Reporting rate of 0.87 cases per million doses administered
- Pfizer-BioNTech COVID-19 vaccine
  - 0 reports following 97.9 million doses administered
- Moderna COVID-19 vaccine
  - 3 reports following 84.7 million doses administered
  - All 3 with normal platelet counts; onset 2, 6, and 12 days after vaccination

Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>

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# CVST with thrombocytopenia following COVID-19 vaccines (conclusions from ACIP April 14, 2021)

Originally presented April 14, 2021

## Summary

- CVST is rare, but clinically serious, and can result in substantial morbidity and mortality; not usually associated with thrombocytopenia
- Observed cases following Janssen COVID-19 vaccines appear to exceed expected based on background rates of CVST among women aged 20–50 years (3-fold or greater)
  - All 6 reports were in women age range 18–48 years, all with thrombocytopenia
  - No obvious patterns of risk factors detected
- CVST with thrombocytopenia has not been observed after the two authorized mRNA vaccines
  - 182 million mRNA COVID-19 doses administered with no reported cases to date
- Clinical features of Janssen cases are similar to those observed following the AstraZeneca COVID-19 vaccine in Europe
- Both Janssen and AstraZeneca vaccines contain replication-incompetent adenoviral vectors (human [Ad26.COV2.S] for Janssen and chimpanzee [ChAdOx1] for AstraZeneca) <sup>24</sup>

**This is an official  
CDC HEALTH ALERT**

Distributed via the CDC Health Alert Network  
April 13, 2021, 1:00 PM ET  
CDCHAN-00442

### **Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine**

#### **Summary**

As of April 12, 2021, approximately 6.85 million doses of the Johnson & Johnson (J&J) COVID-19 vaccine (Janssen) have been administered in the United States. The Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) are reviewing data involving six U.S. cases of a rare type of blood clot in individuals after receiving the J&J COVID-19 vaccine that were reported to the Vaccine Adverse Events Reporting System (VAERS). In these cases, a type of blood clot called cerebral venous sinus thrombosis (CVST) was seen in combination with low levels of blood platelets (thrombocytopenia). All six cases occurred among women aged 18–48 years. The interval from vaccine receipt to symptom onset ranged from 6–13 days. One patient died. Providers should maintain a high index of suspicion for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the J&J COVID-19 vaccine. When these specific type of blood clots are observed following J&J COVID-19 vaccination, treatment is different from the treatment that might typically be administered for blood clots. Based on studies conducted among the patients diagnosed with immune thrombotic thrombocytopenia after the AstraZeneca COVID-19 vaccine in Europe, the pathogenesis of these rare and unusual adverse events after vaccination may be associated with platelet-activating antibodies against platelet factor-4 (PF4), a type of protein. Usually, the anticoagulant drug called heparin is used to treat blood clots. In this setting, the use of heparin may be harmful, and alternative treatments need to be given.

CDC will convene an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on Wednesday, April 14, 2021, to further review these cases and assess potential implications on vaccine policy. FDA will review that analysis as it also investigates these cases. Until that process is complete, CDC and FDA are recommending a pause in the use of the J&J COVID-19 vaccine out of an abundance of caution. The purpose of this Health Alert is, in part, to ensure that the healthcare provider community is aware of the potential for these adverse events and can provide proper management due to the unique treatment required with this type of blood clot.

#### **Background**

VAERS is a national passive surveillance system jointly managed by CDC and FDA that monitors adverse events after vaccinations. The six patients (after 6.85 million vaccine doses administered) described in these VAERS reports came to attention in the latter half of March and early April of 2021 and developed symptoms a median of 9 days (range = 6–13 days) after receiving the J&J COVID-19 vaccine. Initial presenting symptoms were notable for headache in five of six patients, and back pain in the sixth who subsequently developed a headache. One patient also had abdominal pain, nausea, and vomiting. Four developed focal neurological symptoms (focal weakness, aphasia, visual disturbance) prompting presentation for emergency care. The median days from vaccination to hospital admission was 15 days (range = 10–17 days). All were eventually diagnosed with

# Vaccine Safety Datalink (VSD) supplementary analysis for mRNA vaccines

- 2.7 million doses of Pfizer-BioNTech and 2.5 million doses of Moderna COVID-19 vaccine doses administered in VSD as of April 17, 2021
  - 10 total cases of CVST identified following mRNA vaccines
    - 5 cases ruled out (historical n=2, history of head injury n=2, chronic cavernous sinus syndrome n=1)
    - 5 cases potentially CVST, but all without thrombocytopenia
- No confirmed cases of incident CVST with thrombocytopenia after 5.2 million doses of mRNA COVID-19 vaccines administered in VSD

# COVID-19 vaccines and CVST with thrombocytopenia

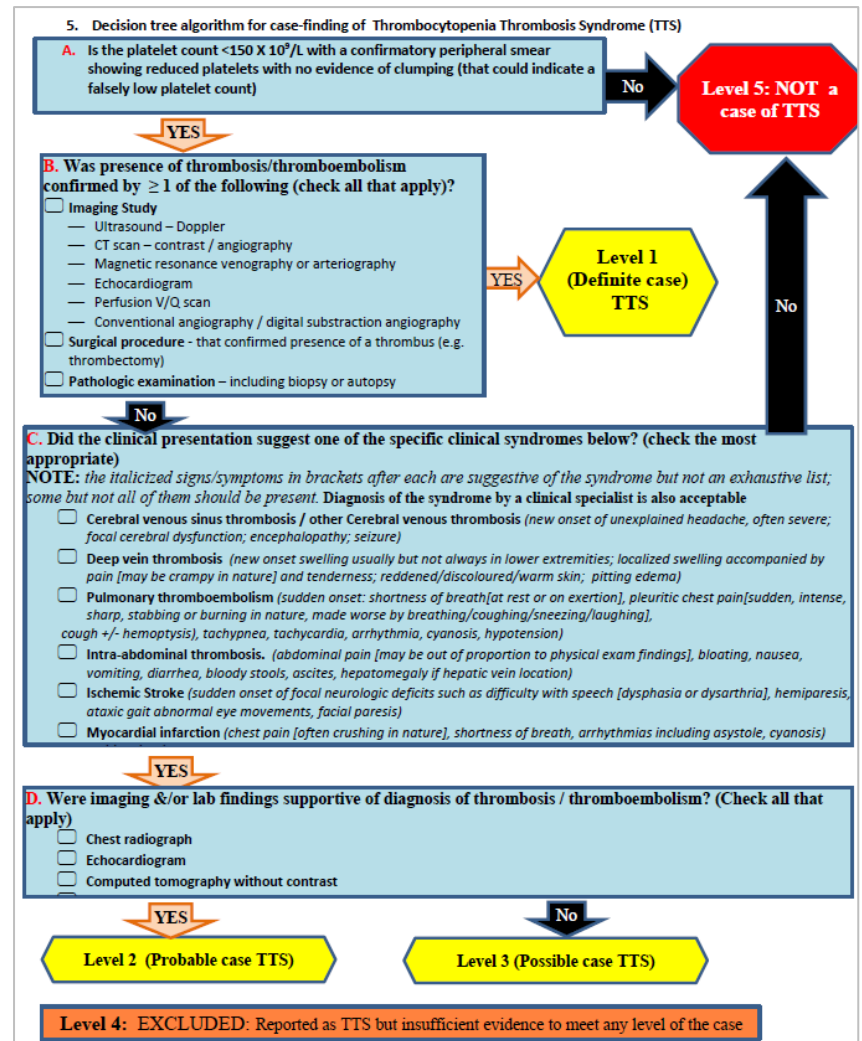
- Safety signal detected for CVST with thrombocytopenia following Janssen COVID-19 vaccine
  - 6 cases observed in women aged 18–48 years in early post-authorization monitoring
  - 1 case observed in pre-authorization clinical trials in a 25-year-old male\*
- Currently, there is a lack of evidence of an association between mRNA COVID-19 vaccines and CVST with thrombocytopenia

\* <https://www.nejm.org/doi/full/10.1056/NEJMc2106075>; <https://www.fda.gov/media/146217/download>

# Brighton Collaboration draft case finding definition for thrombosis with thrombocytopenia syndrome (TTS)

- Platelet count  $<150 \times 10^9/L$
- In addition to rare thromboses, currently includes more common thromboses, such as deep vein thrombosis, pulmonary thromboembolism, ischemic stroke, and myocardial infarction

<https://brightoncollaboration.us/wp-content/uploads/2021/04/TTS-Case-Finding-and-Definition-Process.v9.0-April-16-202115853.pdf>



**Data sources and TTS cases**



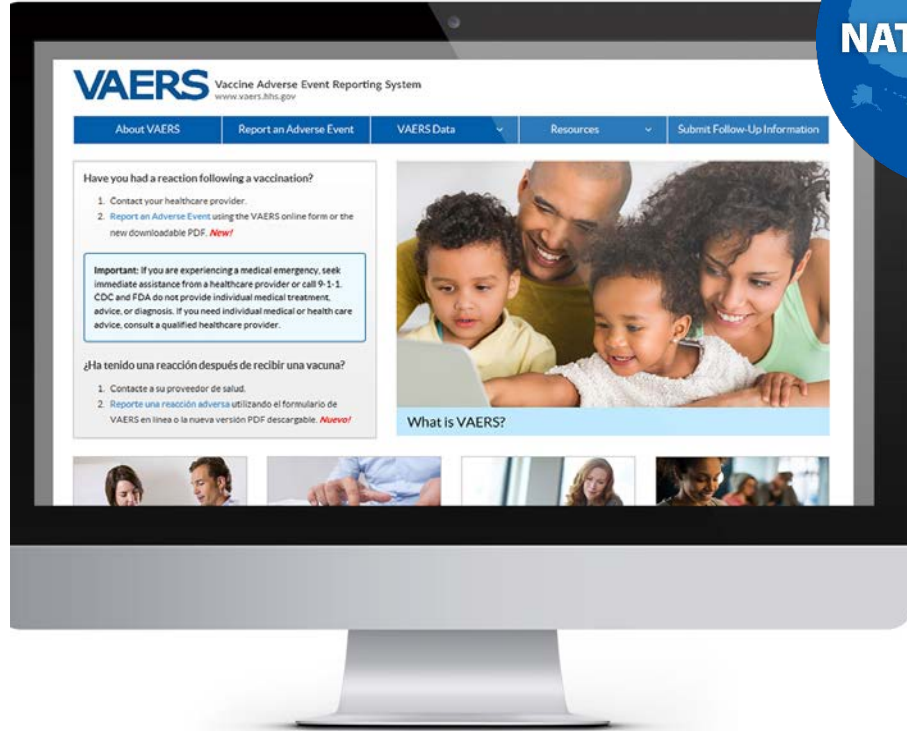
# VAERS is the nation's early warning system for vaccine safety



## VAERS

### Vaccine Adverse Event Reporting System

<http://vaers.hhs.gov>

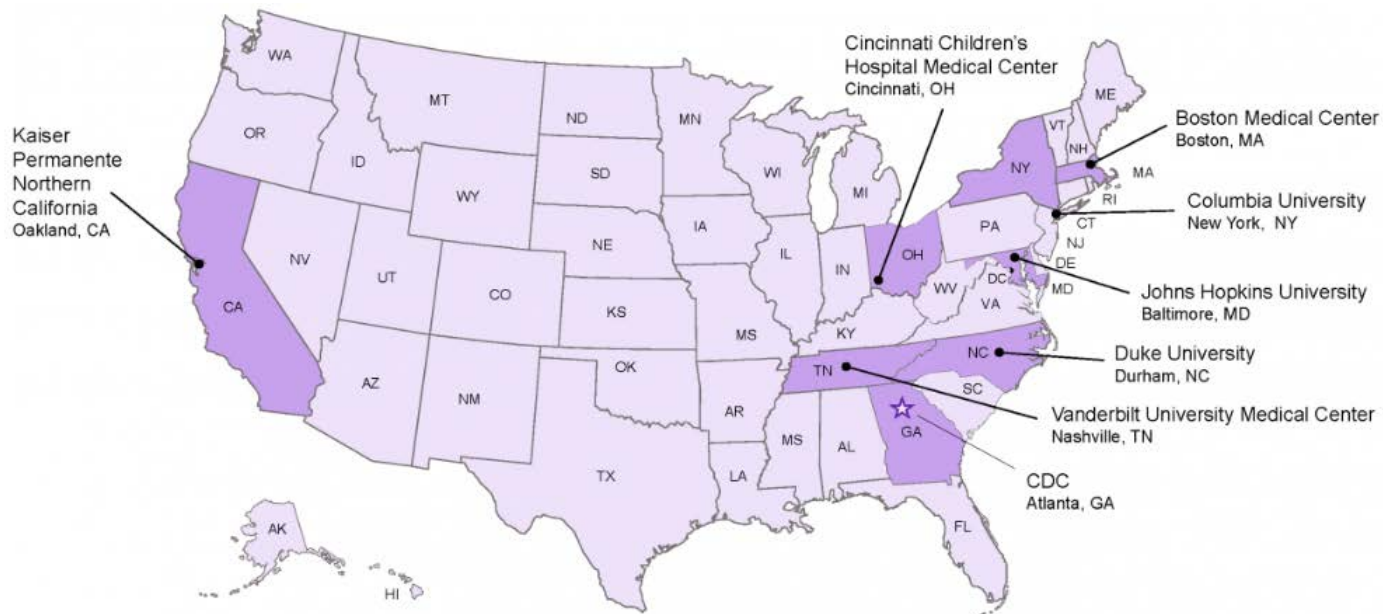




# CISA

## Clinical Immunization Safety Assessment (CISA) Project

7 participating medical research centers with vaccine safety experts



- clinical consult services\*
- clinical research

\*More information about clinical consults available at <http://www.cdc.gov/vaccinesafety/Activities/CISA.html>

# Case finding for TTS following Janssen COVID-19 vaccine

- Healthcare providers directly contact CDC with potential TTS cases
  - CDC initiates an investigation and facilitates submission of a VAERS report
- FDA physicians review incoming VAERS reports daily to identify potential TTS cases
- VAERS database search for possible TTS reports
  - MedDRA PTs for large vessel thrombosis and/or embolism (any report)
  - Did not include the more common thrombosis events\*; these events will be evaluated in subsequent analyses
- Medical records are requested for all potential TTS cases to confirm thrombosis with laboratory evidence of thrombocytopenia
- CDC and FDA medical officers reviewed TTS reports and available medical records; CISA experts including hematologists were consulted

\* e.g., acute myocardial infarction, ischemic stroke, deep vein thrombosis, pulmonary embolism

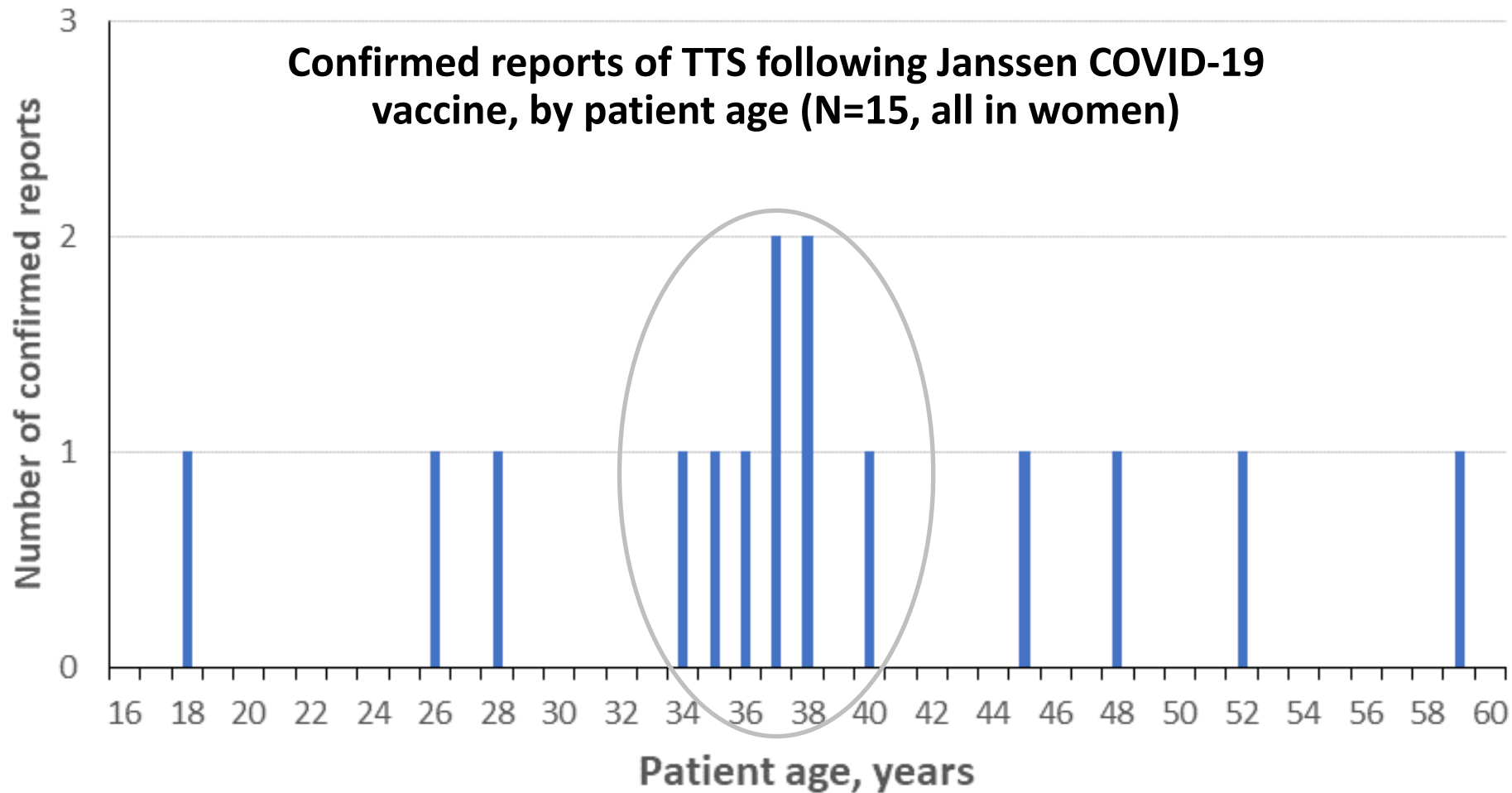
# Reporting rates of TTS after Janssen COVID-19 vaccine

- 7.98 million vaccine doses administered\* and 15 confirmed TTS cases† as of April 21, 2021
  - Some age- and sex-specific doses administered data were imputed
  - Additional potential TTS cases under review, including potential male cases

Age group	Females			Males		
	TTS cases	Doses admin	Reporting rate‡	TTS cases	Doses admin	Reporting rate‡
18-49 years old	<b>13</b>	1,866,294	7.0 per million	<b>0</b>	1,977,330	0 per million
50+ years old	<b>2</b>	2,125,239	0.9 per million	<b>0</b>	2,010,144	0 per million

\* Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>; † One case was excluded from the final analysis: a female aged <50 years who had concurrent diagnosis of COVID-19 and TTS following receipt of Janssen vaccine; ‡ Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

### Confirmed reports of TTS following Janssen COVID-19 vaccine, by patient age (N=15, all in women)



# Reporting rates of TTS after Janssen COVID-19 vaccine in women

- 3.99 million vaccine doses administered to women\* with 15 confirmed TTS cases<sup>†</sup> as of April 21, 2021
  - Some age-specific doses administered data were imputed

	Females		
Age group	TTS cases	Doses admin	Reporting rate <sup>‡</sup>
18-29 years old	3	579,709	5.2 per million
30-39 years old	7	594,215	11.8 per million
40-49 years old	3	692,370	4.3 per million
50-64 years old	2	1,367,529	1.5 per million
65+ years old	0	757,710	0 per million

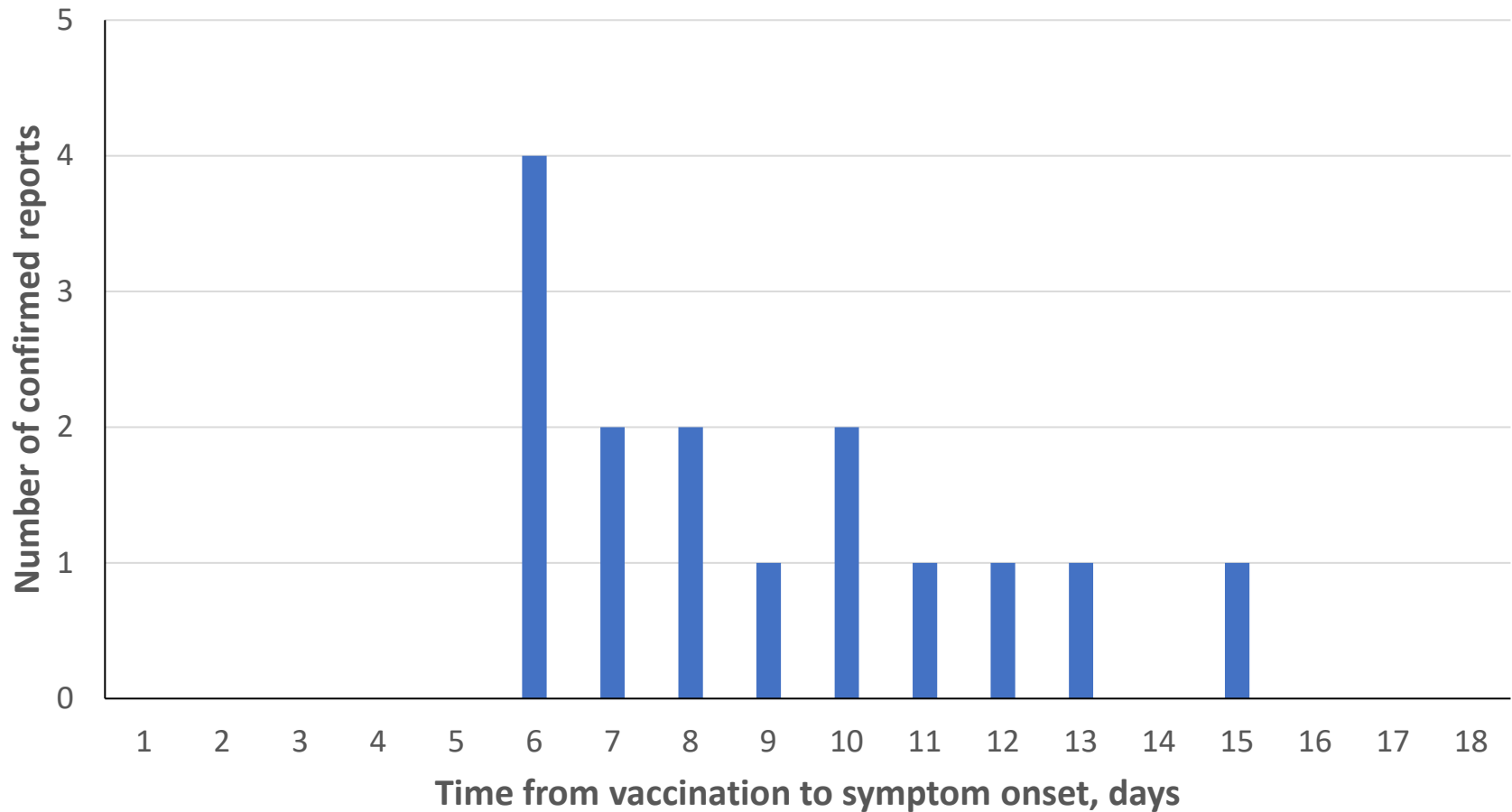
\* Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>; <sup>†</sup> One case was excluded from the final analysis: a female aged <50 years who had concurrent diagnosis of COVID-19 and TTS following receipt of Janssen vaccine; <sup>‡</sup> Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

# Characteristics of patients with TTS after Janssen COVID-19 vaccine, N=15

- Median age 37 years (range 18–59)
- Median time to symptom onset 8 days (range 6–15 days)
- All cases occurred in females
- 12 cases were cerebral venous sinus thrombosis (CVST)
- Pregnant or post-partum\* (n=0)
- COVID-19 disease (n=2); both by history, no documentation of serology testing
- Risk factors for thrombosis<sup>†</sup>
  - Oral contraceptive use (n=2)
  - Obesity (n=7)
  - Hypothyroidism (n=2)
  - Hypertension (n=2)
  - Diabetes (n=0)
  - Coagulation disorders (n=0)

\* Within 12 weeks of delivery; <sup>†</sup> Reference source: <https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis>

## Confirmed Reports of TTS, by Time to Symptom Onset





# Signs and symptoms in patients with cerebral venous sinus thrombosis after Janssen COVID-19 vaccine, N=12

## ■ Initial\*

- Headache (all started  $\geq 6$  days after vaccination)
- Chills
- Fever
- Nausea/vomiting
- Malaise/lethargy
- Abdominal pain

## ■ Later in clinical course\*

- Severe headache, several with neck pain or stiffness
- Nausea/vomiting
- Abdominal pain
- Unilateral weakness
- Speech difficulty
- Gaze deviation
- Loss of consciousness
- Seizure

\* Occurring in  $\geq 2$  patients

# Locations of thromboses in TTP patients, N=15

(not mutually exclusive)

## ■ Cerebral venous sinus locations (n=12)\*

- Transverse sinuses
- Sigmoid sinuses
- Confluence of sinuses
- Straight sinus
- Superior sagittal sinus
- Inferior sagittal sinus
- Cortical veins

## ■ Other locations (n=11)

- Portal vein<sup>†</sup>
- Hepatic vein
- Superior mesenteric artery<sup>†</sup>
- Splenic artery<sup>†</sup>
- Pulmonary artery<sup>†</sup>
- Lower extremity vein<sup>†</sup>
- Internal jugular vein
- Carotid artery<sup>†</sup>
- Brachial vein<sup>†</sup>
- Femoral vein and artery<sup>†</sup>
- Iliac artery<sup>†</sup>

\* 7 patients with cerebral venous sinus thrombosis experienced an intracerebral hemorrhage: temporo-parietal junction, temporal lobe, frontal lobe, occipital lobe, cerebellum, intraventricular, subarachnoid

<sup>†</sup> Patients without CVST had thrombosis in these locations

# Selected laboratory findings in TTS patients, N=15

- **Platelet levels (normal levels: 150,000–450,000 per mm<sup>3</sup>)\***
  - <50,000..... (n=10)
  - 50–<100,000..... (n=3)
  - 100,000–149,000... (n=2)
  
- **PF4 HIT<sup>†</sup> ELISA antibody results**
  - Positive (+)..... (n=11)
  - Negative (-)..... (n=0)
  - Not available..... (n=4)

\* Platelet nadir range: 9,000-127,000; † Platelet factor 4 heparin-induced thrombocytopenia

# SARS-CoV-2 testing results in TTS patients, N=15

## ■ SARS-CoV-2 viral assay

- Negative (n=10)
- Positive (n=0)
- Not available (n=5)

## ■ SARS-CoV-2 serology

- Negative (n=4)
- Positive (n=0)
- Not available (n=11)

# Treatment and outcomes among TTS patients, N=15

## ■ Treatment\*

- Heparin (n=6)<sup>‡</sup>
- Nonheparin anticoagulants (n=12)
- Platelet transfusion (n=7)
- Intravenous immunoglobulin (n=8)

## ■ Outcomes<sup>†</sup>

- Death (n=3)<sup>§</sup>
- Remain hospitalized (n=7)
  - Intensive care unit (n=4)
- Discharged home (n=5)

\* Based on 14 patients

<sup>†</sup> As of April 21, 2021

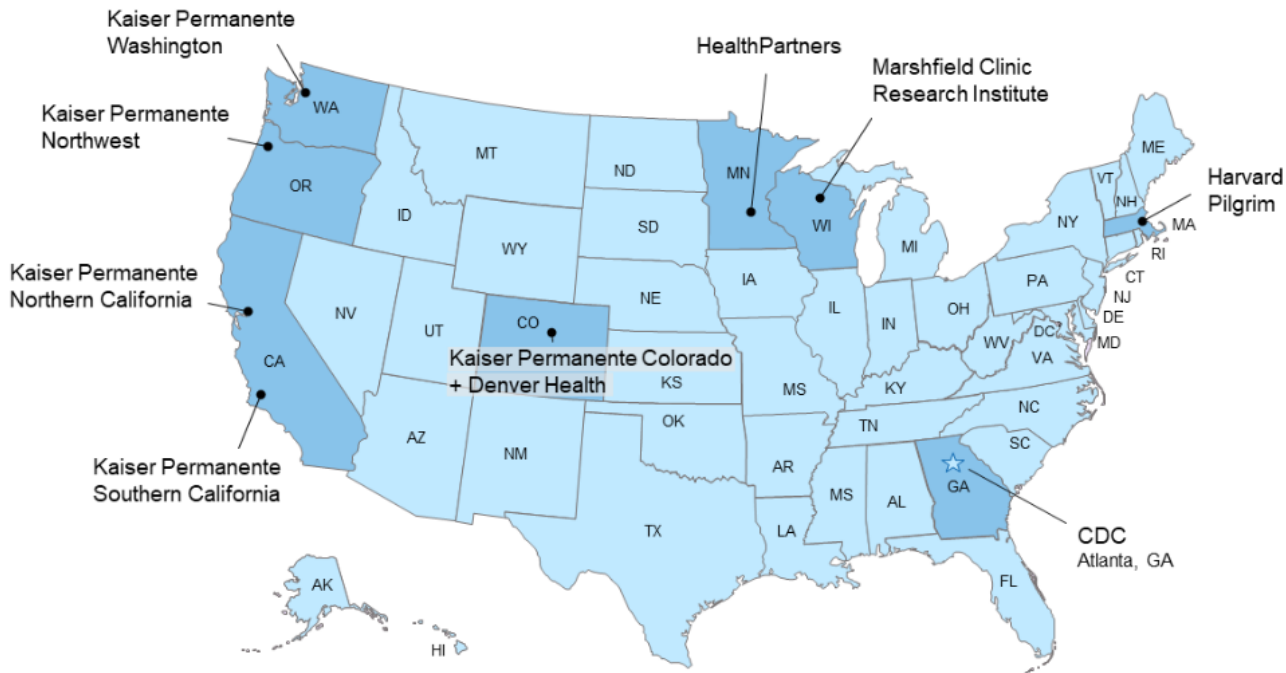
<sup>‡</sup> All patients who received heparin were hospitalized before HAN release

<sup>§</sup> None of the patients who died received heparin



# VSD

## Vaccine Safety Datalink



- 9 participating integrated healthcare organizations
- Data on over 12 million persons per year

# VSD: Thrombosis events after Janssen COVID-19 vaccine

- 142,122 Janssen COVID-19 vaccine doses administered in VSD through April 17, 2021
  - No statistical signals detected for any prespecified Rapid Cycle Analysis outcomes
- No CVST cases identified
- 22 VTE/PE cases identified in the 1–42 days following vaccination and quick reviewed (including 2 with both VTE and PE)
  - 6 ruled out as not VTE
  - 16 were confirmed VTE/PE cases
    - 4 (3 PE, 1 VTE) had symptom onset prior to vaccination
      - Including 1 case with thrombocytopenia documented prior to vaccination
    - 1 had an indeterminate symptom onset
    - 11 were incident cases following vaccination
      - ✓ 6 female (2 PE, 4 VTE), 5 male (1 PE, 4 VTE)
      - ✓ Ages ranged from 50-79 years
      - ✓ None with history of COVID-19 infection
      - ✓ None with thrombocytopenia at time of VTE/PE

VTE = venous thromboembolism

PE = pulmonary embolism

**Summary and next steps**



# Summary

- TTS is a rare, but clinically serious and potentially life-threatening adverse event that has been observed in association with the Janssen COVID-19 vaccine
- Symptom onset appears to occur at least several days after vaccination, typically around 1–2 weeks after vaccination
- The clinical features of TTS following Janssen COVID-19 vaccine appear similar to what is being observed following the AstraZeneca COVID-19 vaccine in Europe
- It is important to recognize TTS early and initiate appropriate treatment
  - Do not treat TTS with heparin, unless HIT testing is negative
- The U.S. vaccine safety monitoring system is able to rapidly detect rare adverse events following immunization and quickly assess safety signals
- Safety surveillance and research on TTS continues
- CDC is committed to open and transparent communication of vaccine safety information

# Next Steps

- Continue enhanced monitoring in VAERS and surveillance in other vaccine safety systems (e.g., VSD, CMS, VA electronic health record)
- Expand VAERS database search strategy for TTS reports (proposed)
  - MedDRA PTs for large vessel thrombosis and embolism (all reports regardless of presence of thrombocytopenia)
  - MedDRA PTs for more common thrombotic events AND MedDRA PTs for thrombocytopenia OR text string for “thrombocytopenia” or “low platelets”
  - Medical record review for all potential TTS cases reports to confirm thrombosis with thrombocytopenia

# How to report an adverse event to VAERS

- Go to [vaers.hhs.gov](https://vaers.hhs.gov)
- Submit a report online
- For help:

Call [1-800-822-7967](tel:1-800-822-7967)

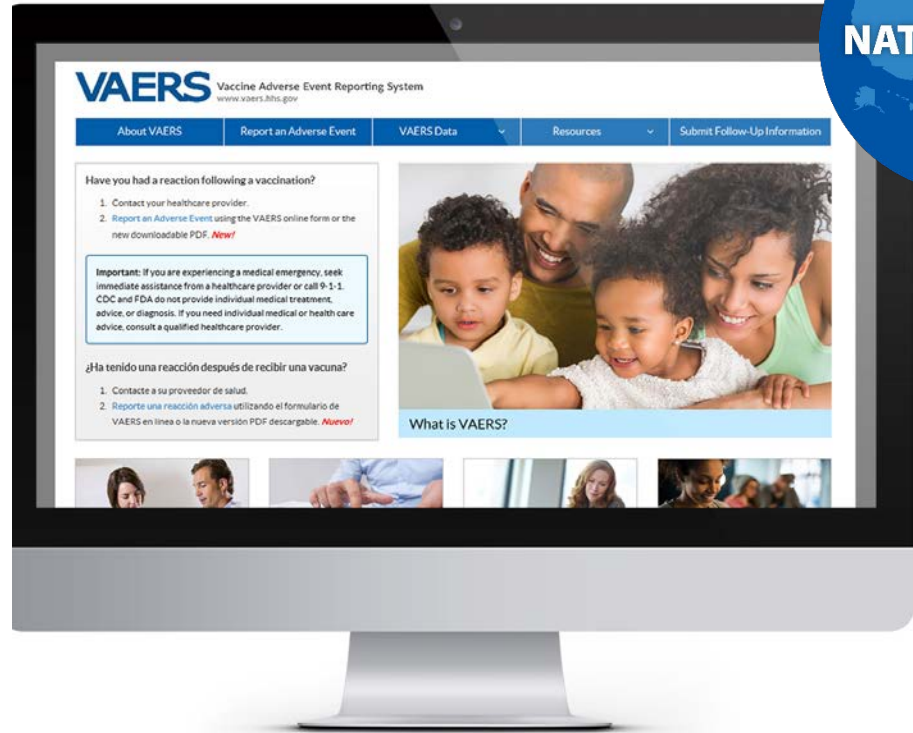
Email [info@VAERS.org](mailto:info@VAERS.org)

video instructions

<https://youtu.be/sbCWWhcQADFE>

- Please send records to VAERS ASAP if contacted and asked

- HIPAA permits reporting of protected health information to public health authorities including CDC and FDA



# Acknowledgments

We wish to acknowledge the contributions of investigators from the following organizations:

## **Centers for Disease Control and Prevention**

COVID-19 Vaccine Task Force

COVID-19 Vaccine Task Force, Vaccine Safety Team

Immunization Safety Office

Division of Healthcare Quality Promotion

Clinical Immunization Safety Assessment Project

Vaccine Safety Datalink

## **Food and Drug Administration**

Center for Biologics Evaluation and Research

**Questions**

**Back-up Slides**

# One report of TTS excluded from case count

- Female aged <50 years with COVID-19 (PCR positive) and TTS with complex clinical course:
  - Received Janssen vaccine
  - Hospitalization 1 (admitted 22 days after vaccination): for COVID-19 pneumonia
    - Presented with nausea, hematemesis, shortness of breath; date of symptom onset unclear
    - Normal platelet count
  - Hospitalization 2 (readmitted 28 days after vaccination):
    - Presented with nausea, hematemesis, abdominal pain, shortness of breath, cough
    - Platelet 100,000
    - Imaging studies showed CVST, lower leg venous thromboembolism, pulmonary embolism
    - Died during hospitalization\*

\*Reported cause of death: respiratory failure, shock, COVID-19 pneumonia

# Proposed VAERS MedDRA PT and text string search terms for TTS

## ▪ MedDRA PTs for large vessel thrombosis and embolism

- Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis

## ▪ MedDRA PTs for more common thrombotic events

- Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, MedDRA PTs for acute myocardial infarction\*, MedDRA PTs for stroke\*

## ▪ MedDRA PTs for thrombocytopenia

- Autoimmune heparin-induced thrombocytopenia, Heparin-induced thrombocytopenia, Immune thrombocytopenia, Non-immune heparin associated thrombocytopenia, Spontaneous heparin-induced thrombocytopenia syndrome, Thrombocytopenia, Thrombocytopenic purpura

## ▪ Text string for

- “thrombocytopenia” or “low platelets” in symptom text

\* <https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf>