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

Advisory Committee on Immunization Practices (ACIP)
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Topics

- Background
- Reports of cerebral venous sinus thrombosis (CVST) with thrombocytopenia (low platelets) following Janssen COVID-19 vaccine
- Summary

Background

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

* Source: https://www.mayoclinic.org/diseases-conditions/thrombocytopenia/symptoms-causes/syc-20378293

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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).

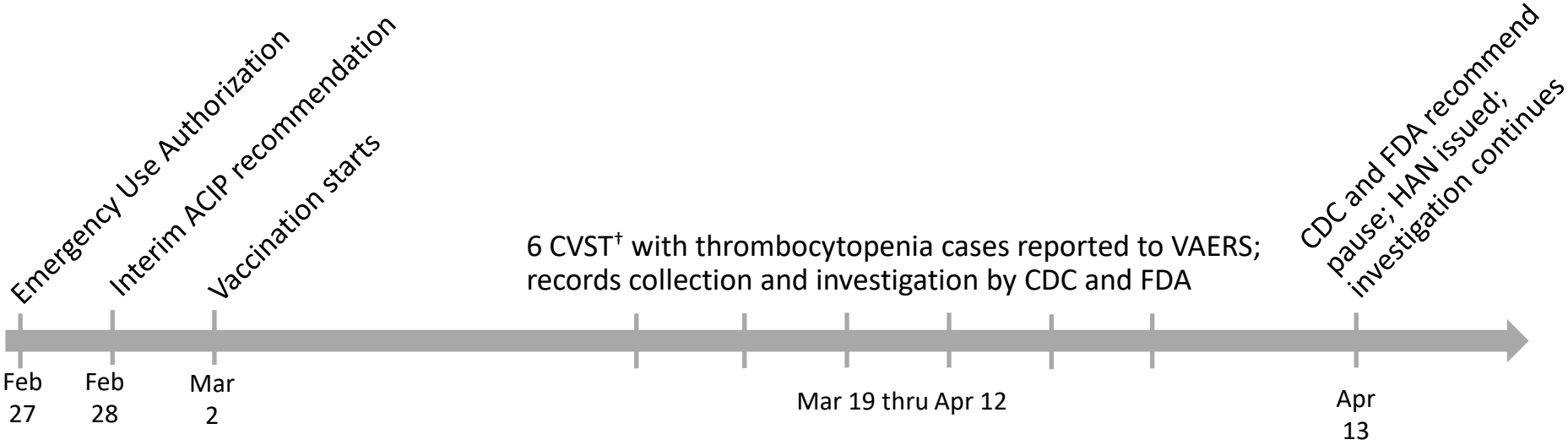
The PRAC noted that the blood clots occurred in veins in the brain (cerebral venous sinus thrombosis, CVST) and the abdomen (splanchnic vein thrombosis) and in arteries, together with low levels of blood platelets and sometimes bleeding.

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.[1] 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.

https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

Janssen COVID-19 vaccine timeline* (2021)



* For illustrative purposes, not drawn to scale, † cerebral venous sinus thrombosis

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 suspension 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

https://emergency.cdc.gov/han/2021/han00442.asp

Cerebral venous sinus anatomy

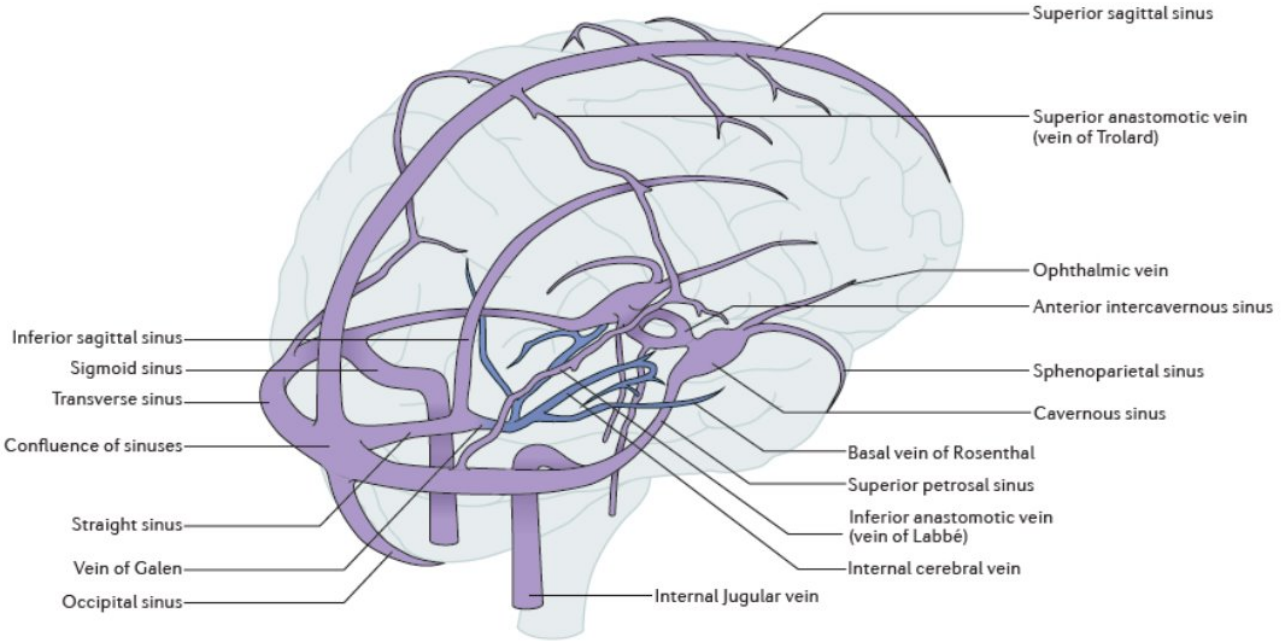


Figure 1 | **Anatomy of the cerebral venous system.** Diagram showing the main components of the cerebral venous system. Blue vessels represent the deep venous system.

Silvis SM et al, Nature Reviews Neurology 13, 555-565(2017)

Cerebral venous sinus thrombosis (CVST)

Background epidemiology[1-3]

- Rare, 0.22–1.57 per 100,000, ~0.5-1% of all strokes
- Median age 37 years
- 8% of patients >65 years
- Female:male ratio of 3:1

Risk factors[4]

- Prothrombotic conditions (genetic or acquired)
- Oral contraceptives
- Pregnancy and the post-partum period
- Malignancy
- Infection
- Mechanical precipitants (lumbar puncture)

[1] Cerebral vein and dural sinus thrombosis in Portugal: 1980-1998. Ferro JM, Correia M, Pontes C, Baptista MV, Pita F, Cerebral Venous Thrombosis Portuguese Collaborative Study Group (Venoport) Cerebrovasc Dis. 2001;11(3):177.
[2] The incidence of cerebral venous thrombosis: a cross-sectional study. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. Stroke. 2012 Dec;43(12):3375-7..
[3] Cerebral Venous Sinus Thrombosis Incidence Is Higher Than Previously Thought: A Retrospective Population-Based Study. Devasagayam S, Wyatt B, Leyden J, Kleinig T. Stroke. 2016 Sep;47(9):2180-2.
[4] Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Saposnik G, et al. 2011;42(4):1158.

CVST signs and symptoms

- More common presentations
  - Isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema, and visual problems)
  - Focal syndrome (focal deficits, seizures, or both)
  - Encephalopathy (multifocal signs, mental status changes, stupor, or coma)

- Rare presentations
  - Cavernous sinus syndrome
  - Subarachnoid hemorrhage
  - Cranial nerve palsies

Data source and case reports

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

CDC + FDA

VAERS

Vaccine Adverse Event Reporting System

http://vaers.hhs.gov

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 <150K/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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  - All 3 with normal platelet counts (150–450K/mm3)

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Characteristics of patients with CVST and thrombocytopenia* after Janssen COVID-19 vaccine, N=6

- Median age 33 years (range 18–48)
- Median time to symptom onset 8 days (range 6–13 days)
- All cases occurred in white females
- Current estrogen/progesterone use (n=1)
- Pregnant or post-partum (n=0)
- Pre-existing conditions
  - Obesity (n=3)
  - Hypothyroidism (n=1)
  - Hypertension (n=1)
  - Asthma (n=1)
  - Coagulation disorders (none known)

* Note: Thrombosis usually does not occur in the presence of low platelets; these case presentations are atypical and consistent with cases observed after AstraZeneca COVID-19 vaccine

Initial and late signs and symptoms among CVST patients*, N=6 (patients listed in no particular order)

	Initial features	Late features
Patient 1	Headaches, lethargy	Severe headache, left-sided weakness, vomiting
Patient 2	Headaches	Severe headache, aphasia
Patient 3	Headaches, vomiting, fever	Left arm weakness, right gaze deviation, left neglect
Patient 4	Headaches, chills, myalgias	Severe abdominal pain and fever
Patient 5	Headache, chills, dyspnea, fever	Bruising, unilateral leg swelling, loss of consciousness
Patient 6	Back pain, bruising	Headache, abdominal pain

*All were hospitalized and admitted to the intensive care unit

Locations of CVST, intracerebral hemorrhage, and other thromboses, N=6

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Location of CVST	Right transverse sinus and right sigmoid sinus	Left transverse sinus, left sigmoid sinus, confluence of sinuses, and straight sinus	Superior sagittal sinus, inferior sagittal sinus, and straight sinus	Right transverse sinus and right sigmoid sinus	Right transverse sinus and right sigmoid sinus	Right transverse sinus
Location of intracerebral hemorrhage	Right temporo-parietal lobe	Left temporal lobe	Bilateral frontal lobes, intraventricular	None	None	Occipital lobe
Locations of other thromboses	None	None	None	**Portal vein and right pulmonary artery**	**Bilateral lower extremity VTE, right internal jugular vein**	**Portal vein**

SARS-CoV-2 test results among CVST patients, N=6

	SARS-CoV-2 viral test	SARS-CoV-2 serology
Patient 1	Negative	Not documented
Patient 2	Negative	Nucleocapsid Ab negative
Patient 3	Negative	Not documented
Patient 4	Negative	Not documented
Patient 5	Negative	Unspecified COVID Ab negative
Patient 6	Negative	Unspecified COVID Ab negative

Hematology test results among CVST patients, N=6

	Lowest platelet value (per mm^3)	PF4 HIT* antibody test result(s)
Patient 1	12,000	Not done
Patient 2	69,000	Positive
Patient 3	18,000	Positive
Patient 4	127,000	Positive
Patient 5	10,000	Positive
Patient 6	14,000	Positive

*Platelet factor 4 heparin induced thrombocytopenia

Treatment and outcomes among CVST patients, N=6

- Treatment
  - Heparin (n=4)
  - Nonheparin anticoagulants (n=5)
  - Platelets (n=3)
  - Intravenous immunoglobulin (n=3)
- Outcomes
  - Death (n=1)
  - Remain hospitalized (n=3)
    - Intensive care unit (n=2)
  - Discharged home (n=2)

* All 5 of these patients received Argatraban

Observed vs. expected CVST cases following Janssen COVID-19 vaccine

- Estimated annual incidence of CVST ~0.5–2 cases per 100,000 population*
- Assumed risk period of 5.6% of a calendar year: (41 days/2) ÷ 365 days
- Doses administered among women aged 20–50 years = 1,402,712 doses (as of Apr 12)

Est. annual background incidence	Expected cases in women aged 20–50 yrs	Reporting ratio, women aged 20–50 yrs
0.5 per 100K	0.39	**15.2**
1.0 per 100K	0.79	**7.6**
1.5 per 100k	1.18	**5.1**
2.0 per 100k	1.58	**3.8**

* https://www.hopkinsmedicine.org/health/conditions-and-diseases/cerebral-venous-sinus-thrombosis, http://www.med.umich.edu/1libr/Stroke/SinusVeinThrombosis.pdf, https://www.nejm.org/doi/10.1056/NEJMra042354?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub, https://www.ahajournals.org/doi/pdf/10.1161/STROKEAHA.116.013617, https://www.nature.com/articles/nrneurol.2017.104

Summary

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)

Summary (cont.)

- **For clinicians**
  - Maintain a high index of suspicion for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the Jansen COVID-19 vaccine, including severe headache, backache, new neurologic symptoms, severe abdominal pain, shortness of breath, leg swelling, petechiae (tiny red spots on the skin), or new or easy bruising. Obtain platelet counts and screen for evidence of immune thrombotic thrombocytopenia.
  - In patients with a thrombotic event and thrombocytopenia after the Jansen COVID-19 vaccine, evaluate initially with a screening PF4 enzyme-linked immunosorbent (ELISA) assay as would be performed for autoimmune HIT. Consultation with a hematologist is strongly recommended.
  - Do not treat patients with thrombotic events and thrombocytopenia following receipt of Janssen COVID-19 vaccine with heparin, unless HIT testing is negative.
  - If HIT testing is positive or unable to be performed in patient with thrombotic events and thrombocytopenia following receipt of Jansen COVID-19 vaccine, non-heparin anticoagulants and high-dose intravenous immune globulin should be strongly considered.
  - Report adverse events to VAERS, including serious and life-threatening adverse events and deaths in patients following receipt of COVID-19 vaccines as required under the Emergency Use Authorizations for COVID-19 vaccines.

Summary (cont.)

- **For public health**
  - Encourage healthcare providers and the public to report all serious and life-threatening adverse events and deaths following receipt of COVID-19 vaccines to VAERS as required under the EUAs for COVID-19 vaccines.
  - Disseminate information to healthcare providers in your jurisdictions.
- **For the public**
  - If you have received the Janssen COVID-19 vaccine and develop severe headache, abdominal pain, leg pain, or shortness of breath within three weeks after vaccination, contact your healthcare provider, or seek medical care.
  - Report adverse events following receipt of any COVID-19 vaccine to VAERS.
  - If you are scheduled to receive the Janssen vaccine, please contact your healthcare provider, vaccination location, or clinic to learn about additional vaccine availability.

How to report an adverse event to VAERS

- Go to vaers.hhs.gov
- Submit a report online
- For help:

  Call 1-800-822-7967

  Email info@VAERS.org

  video instructions https://youtu.be/sbCWhcQADFE

- 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

Next steps

- Continue enhanced monitoring in VAERS and other vaccine safety systems (e.g., Vaccine Safety Datalink [VSD])
  - VSD: ~113K Janssen doses administered, 0 cases in risk interval(s)
- Investigate potential cases through detailed clinical reviews/chart reviews
- Refine analyses to better quantify risk

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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 Adverse Event Safety Network

Questions