



Update on Thrombosis with Thrombocytopenia Syndrome (TTS)

Isaac See, MD on behalf of CISA Project

December 6, 2021

Disclaimer

- The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the CDC
- These slides contain confidential information

Outline

- Background
- Update on epidemiology of U.S. TTS cases after Janssen COVID-19 Vaccine
- Focus on U.S. TTS deaths after Janssen COVID-19 Vaccine

- Earlier version of data presented here available on medRxiv (<https://www.medrxiv.org/content/10.1101/2021.11.10.21266063v1>)

Background

Cerebral Venous Sinus Thrombosis (CVST) background

- “CVST is a potentially fatal neurological condition that is often under-diagnosed due to its nonspecific presentation.”¹
- Acute death from CVST usually caused by brain herniation secondary to large hemorrhagic lesion, followed by herniation due to multiple lesions or to diffuse brain edema
- Reported prognostic factors for poor short-term outcome include
 - Anatomical: brain herniation, hemorrhage, posterior fossa lesions
 - Clinical presentation: status epilepticus, depressed consciousness, altered mental status

1. Idiculla PS et al. Cerebral Venous Thrombosis: a comprehensive review. Eur Neuro 2020;83:369-379.

Saposnik G, et al. AHA/ASA scientific statement. Diagnosis and management of cerebral venous thrombosis. Stroke 2011;42:1158-1192.

Timeline for initial U.S. events for TTS following Janssen COVID-19 Vaccine, 2021

First post-authorization U.S. doses of Janssen COVID-19 Vaccine

FDA authorizes Janssen COVID-19 Vaccine

CDC/FDA announce pause in use of Janssen COVID-19 Vaccine after identification of 6 cases of CVST with thrombocytopenia

ACIP reviews data

Benefit/risk analysis: in states with “low” COVID-19 incidence, **2 COVID-19 deaths per million Janssen doses prevented** within 30 days of vaccination for women <50 years of age

Feb 27

Mar 2

Apr 13

Apr 23

<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>

<https://www.fda.gov/media/146304/download>

Timeline for initial U.S. events for TTS following Janssen COVID-19 Vaccine, 2021

First post-authorization U.S. doses of Janssen COVID-19 Vaccine

FDA authorizes Janssen COVID-19 Vaccine

CDC/FDA announce pause in use of Janssen COVID-19 Vaccine after identification of 6 cases of CVST with thrombocytopenia

ACIP reviews data

Reaffirms recommendation for Janssen COVID-19 Vaccine

Benefit/risk analysis: in states with “low” COVID-19 incidence, **2 COVID-19 deaths per million Janssen doses prevented** within 30 days of vaccination for women <50 years of age

CDC interim clinical considerations and FDA EUA fact sheets updated with information about risk of TTS particularly in women <50 years of age

Feb 27

Mar 2

Apr 13

Apr 23

<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>

<https://www.fda.gov/media/146304/download>

Case finding in VAERS for TTS following COVID-19 vaccines

- VAERS database search conducted daily for possible TTS reports
 - Healthcare providers directly contacted CDC with potential TTS
 - CDC initiates an investigation and facilitates submission of a VAERS report
- Medical records requested for all potential TTS case reports to confirm thrombosis with laboratory evidence of thrombocytopenia, using working case definition, reviewed by CDC and FDA medical officers
- Clinical Immunization Safety Assessment (CISA) experts including hematology/neurology confirm clinical syndrome consistent with TTS and rule-out other causes of thrombosis and thrombocytopenia.



CDC working case definition for TTS following COVID-19 Vaccine

| TTS category | Thrombosis location | Platelet count | Positive PF4 ELISA test required? |
|--------------|--|----------------------|-----------------------------------|
| Tier 1 | Unusual location, e.g., CVST, splanchnic venous or arterial thrombosis | <150K cells/ μ L | No |
| Tier 2 | Only in 'typical' location(s), e.g., pulmonary embolism, deep vein thrombosis of extremity | <150K cells/ μ L | Yes |

- Reports where only thrombosis is ischemic stroke or myocardial infarction are excluded
- Cases with concurrent COVID-19 infection excluded

Analytic period

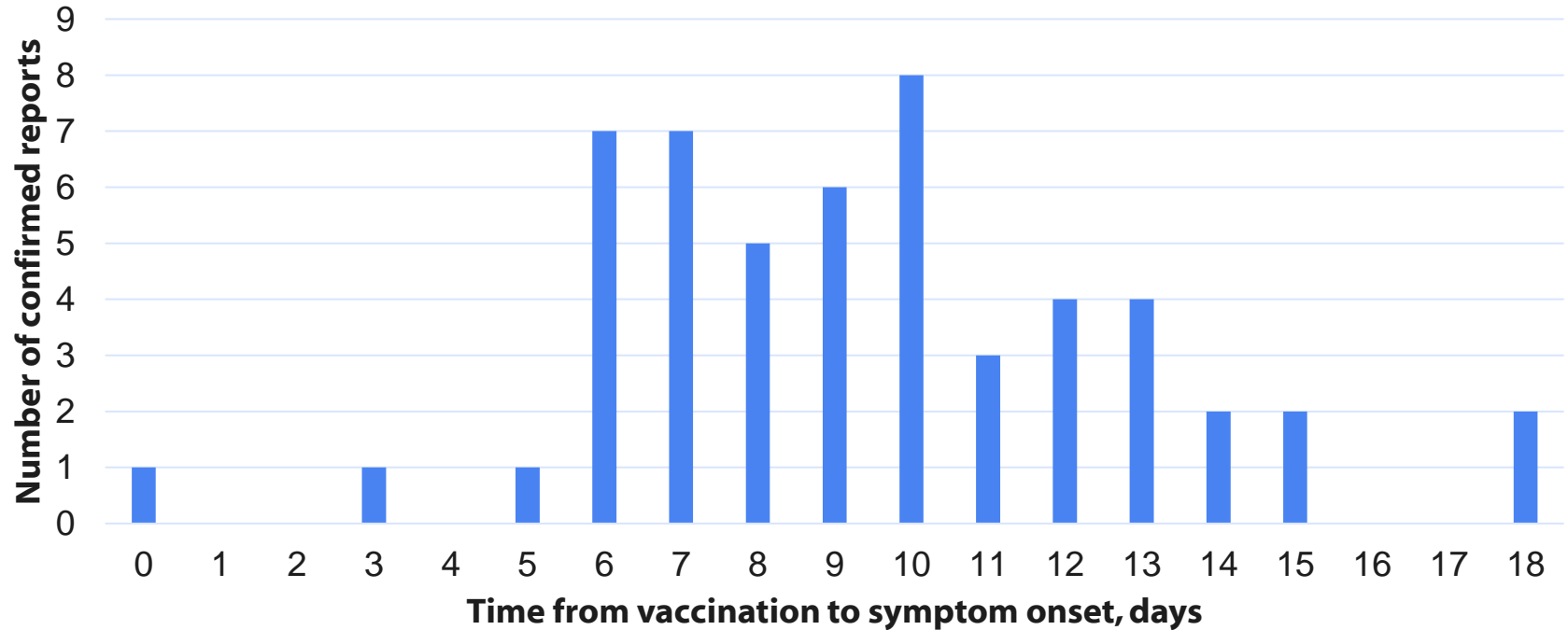
- Descriptive epidemiology and reporting rates for TTS cases receiving Janssen COVID-19 Vaccine through August 31, 2021
- Summarize information about all deaths among TTS cases following Janssen COVID-19 Vaccine confirmed by December 2, 2021
 - Death reporting rates through August 31, 2021

**Epidemiology of U.S. TTS cases with
Janssen COVID-19 vaccination through
August 31, 2021**

Characteristics of U.S. TTS cases after Janssen COVID-19 vaccination, N=54 (Tier 1=46, Tier 2=8)

- Median age: 44.5 years (range 18-70 years)
 - 26 (48%) are women aged <50 years
- Median time from vaccination to symptom onset: 9 days (range 0-18 days)
- Median time from symptom onset to admission: 5 days (range: 0-30 days)
- 39 (72%) received the Janssen COVID-19 Vaccine before the pause on April 13, 2021
- All after dose 1 of Janssen COVID-19 Vaccine
- Female (n=37), male (n=17)
- 29 of the TTS cases (54%) have a cerebral venous sinus thrombosis (CVST)
- Pregnant or postpartum (n=0)
- Known or newly diagnosed thrombophilia (n=0)
- Past SARS-CoV-2 infection (n=7); 5 by history, 2 by nucleocapsid serology testing only

Time from Janssen COVID-19 vaccination to symptom onset, (N=53*)



*Exact symptom onset could not be determined for one case but known to be ≤ 12 days after vaccination

Venous thrombosis risk factors in U.S. TTS cases following Janssen COVID-19 vaccination, N=54 (not mutually exclusive)

| Risk factor | n (%) |
|---------------------------------------|---------|
| Obesity | 25 (46) |
| Hypertension | 16 (30) |
| Diabetes | 7 (13) |
| Systemic estrogen therapy* | 3 (6) |
| Other venous thrombosis risk factor** | 3 (6) |

*2 receiving combined oral contraceptives and 1 on estradiol patch for hormone replacement therapy

**Other venous thrombosis risk factors include cirrhosis, malignancy, fertility treatment, venous catheter at thrombosis site; one case had both venous catheter at thrombosis site and malignancy

Outcomes among U.S. TTS cases following Janssen COVID-19 vaccination, N=54

- All hospitalized
- ICU admission (n=36)
- Length of stay for patients discharged alive:
 - Median 9 days
 - Range: 1-132 days
- **Outcome of hospitalization**
 - Death (n=8)
 - Discharged to post-acute care facility (n=9)
 - Discharged home (n=37)

Reporting rates of TTS after Janssen COVID-19 vaccine, vaccination through August 31, 2021 (N=54)

14.1 million total Janssen COVID-19 vaccine doses administered*

| Age group | Females | | | Males | | |
|---------------|-----------|-------------|---|-----------|-------------|---|
| | TTS cases | Doses admin | Reporting rate [†] (per million) | TTS cases | Doses admin | Reporting rate [†] (per million) |
| 18-29 yrs old | 5 | 1,089,649 | 4.59 | 3 | 1,565,212 | 1.92 |
| 30-39 yrs old | 11 | 1,037,386 | 10.60 | 3 | 1,443,900 | 2.08 |
| 40-49 yrs old | 10 | 1,108,495 | 9.02 | 6 | 1,392,990 | 4.30 |
| 50-64 yrs old | 9 | 2,002,984 | 4.49 | 5 | 2,338,263 | 2.14 |
| 65+ yrs old | 2 | 1,096,923 | 1.82 | 0 | 1,004,285 | 0 |

Overall reporting rate: 3.83 cases per million Janssen doses

* Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>; † Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

Reporting rates of TTS after Janssen COVID-19 vaccine, females: comparing July ACIP rates to current

| Age group | Females (Jul ACIP*) | | | Females (Current**) | | |
|---------------|---------------------|------------------|---|---------------------|------------------|---|
| | TTS cases | Doses admin | Reporting rate [†] (per million) | TTS cases | Doses admin | Reporting rate [†] (per million) |
| 18-29 yrs old | 4 | 946,358 | 4.22 | 5 | 1,089,649 | 4.59 |
| 30-49 yrs old | 17 | 1,934,574 | 8.79 | 21 | 2,145,881 | 9.79 |
| 50-64 yrs old | 7 | 1,865,372 | 3.75 | 9 | 2,002,984 | 4.49 |
| 65+ yrs old | 0 | 1,028,190 | 0 | 2 | 1,096,923 | 1.82 |
| Total | 28 | 5,774,494 | 4.85 | 37 | 6,335,437 | 5.84 |

* Jul ACIP: vaccination through Jul 8, 2021 <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/05-COVID-Rosenblum-508.pdf>

** Current data: vaccination through August 31, 2021

• Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>; [†] Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

Reporting rates of TTS after Janssen COVID-19 vaccine, males: comparing July ACIP rates to current

| Age group | Males (Jul ACIP*) | | | Males (current**) | | |
|---------------|-------------------|------------------|---|-------------------|------------------|---|
| | TTS cases | Doses admin | Reporting rate [†] (per million) | TTS cases | Doses admin | Reporting rate [†] (per million) |
| 18-29 yrs old | 3 | 1,281,479 | 2.34 | 3 | 1,565,212 | 1.92 |
| 30-49 yrs old | 4 | 2,440,773 | 1.64 | 9 | 2,836,890 | 3.17 |
| 50-64 yrs old | 3 | 2,130,473 | 1.41 | 5 | 2,338,263 | 2.14 |
| 65+ yrs old | 0 | 943,098 | 0 | 0 | 1,004,285 | 0 |
| Total | 10 | 6,795,823 | 1.47 | 17 | 7,744,650 | 2.20 |

* Jul ACIP: vaccination through Jul 8, 2021 <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/05-COVID-Rosenblum-508.pdf>

** Current data: vaccination through August 31, 2021

• Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>; [†] Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

**TTS Deaths following Janssen Vaccination
Confirmed as of December 2, 2021**

Demographics/comorbidities of TTS deaths following Janssen through December 2, 2021 (N=9*)

- All after dose 1 of Janssen COVID-19 Vaccine
- Median age: 45 years (range: 28-62)
- Sex: female (n=7), male (n=2)
- Race/ethnicity: all non-Hispanic white
- Underlying medical conditions:
 - Obesity (n=7)
 - Hypertension (n=3)
 - Diabetes (n=2)
 - **None of the above (n=2)**
 - Iron deficiency anemia (n=2)
 - Hypothyroidism (n=2)
 - Other** (n=4)

* One TTS death confirmed in a person vaccinated with Janssen COVID-19 Vaccine after August 31, 2021

** Other includes (n=1 each) asthma, gastroesophageal reflux disease, obstructive sleep apnea, hyperlipidemia, seizure disorder; one patient with both hyperlipidemia and seizure disorder

Clinical description of TTS deaths following Janssen through December 2, 2021 (N=9)

- All have features of severe CVST: large or multiple cerebral hemorrhages; evidence of intracranial edema and/or mass effect; depressed consciousness and/or seizure
- 7 with confirmed CVST
- Three were previously discharged from emergency department with potential TTS symptoms
- None received IV heparin for treatment
- Four received craniectomy/craniotomy for brain hemorrhage
- Median time from symptom onset to admission: 3 days (range: 0-5)
- Median time from admission to death: 1 day (range: 0-2)

Revisit TTS updates to ACIP

| Date of meeting | Purpose of discussion | Cut-off for data | Janssen doses | TTS cases | TTS deaths |
|-----------------|---|------------------|---------------|-----------|------------|
| Apr 23 | Discuss resolution of Janssen Pause | Apr 21 | 7.98 million | 15 | 3 |
| May 12 | General follow-up on TTS | May 7 | 8.73 million | 28 | 3 |
| Jul 22 | Updated benefit-risk discussion (including GBS) | Jul 8 | 12.5 million | 38 | 4 |

Revisit TTS updates to ACIP

| Date of meeting | Purpose of discussion | Cut-off for data | Janssen doses | TTS cases | TTS deaths |
|-----------------|---|------------------|---------------|----------------------------|--------------------------|
| Apr 23 | Discuss resolution of Janssen Pause | Apr 21 | 7.98 million | 15 39 | 3 5 |
| May 12 | General follow-up on TTS | May 7 | 8.73 million | 28 43 | 3 6 |
| Jul 22 | Updated benefit-risk discussion (including GBS) | Jul 8 | 12.5 million | 38 50 | 4 6 |
| Dec 6 | Update VaST | Aug 31 | 14.1 million | 54 | 8 |

TTS Death reporting rate with Janssen COVID-19 Vaccine by August 31, 2021 (N=8 confirmed deaths)

Overall death reporting rate: 0.57 per million Janssen COVID-19 Vaccine doses

| Age group | Females | | | Males | | |
|---------------|------------|------------------|---|------------|------------------|---|
| | TTS deaths | Doses admin | Reporting rate [†] (per million) | TTS deaths | Doses admin | Reporting rate [†] (per million) |
| 18-29 yrs old | 0 | 1,089,649 | 0 | 1 | 1,565,212 | 0.64 |
| 30-39 yrs old | 2 | 1,037,386 | 1.93 | 0 | 1,443,900 | 0 |
| 40-49 yrs old | 2 | 1,108,495 | 1.80 | 1 | 1,392,990 | 0.72 |
| 50-64 yrs old | 2 | 2,002,984 | 1.00 | 0 | 2,338,263 | 0 |
| 65+ yrs old | 0 | 1,096,923 | 0 | 0 | 1,004,285 | 0 |
| Total | 6 | 6,335,437 | 0.95 | 2 | 7,744,650 | 0.26 |

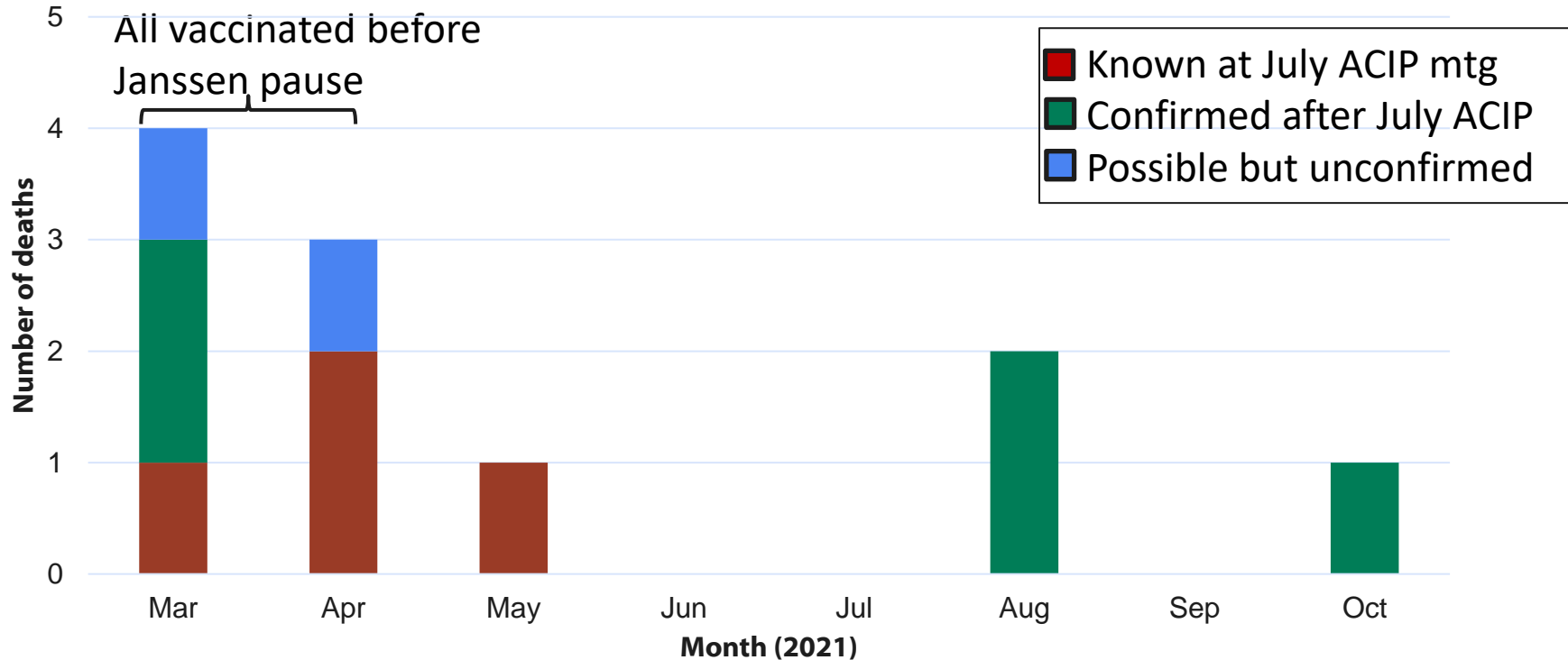
*Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>; [†] Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

Two additional possible TTS deaths with Janssen COVID-19 vaccination before pause

- Features shared with confirmed TTS deaths after Janssen
 - Symptoms beginning within 7-14 days of vaccination
 - Large cerebral hemorrhage with mass effect and thrombocytopenia
 - Rapid progression from admission to death (1-2 days)
- Difference: no definitive imaging for CVST; no imaging for other thrombosis
- Reviewed with CISA investigators
 - Difficult to confirm as TTS cases because of lack of documented thrombosis
 - Clinically concerned that TTS with CVST is underlying cause of death

Of the two additional possible TTS deaths following Janssen COVID-19 vaccination, 1 is in a woman between 50-64 years of age and the other in a man 40-49 years

TTS confirmed and possible deaths following Janssen COVID-19 Vaccine to date*, by month of vaccination



*Confirmed as of Dec 2, 2021

Limitations

- Possible underdiagnosis of CVST
- VAERS is passive surveillance system
- **Case and death reporting rates might be underestimates**

Summary

- U.S. TTS case reporting rate following Janssen COVID-19 vaccination higher than previously presented
 - Case reporting rate for men 40-49 years and women 50-64 years similar to women 18-29 years
- U.S. TTS deaths following Janssen COVID-19 vaccination:
 - Have typical features of severe CVST
 - Clinical course from symptoms to admission, and admission to death is rapid
 - Are more common than known during previous presentations to ACIP (TTS death reporting rate following Janssen: ~2 per million doses in women 30-49 years)

Acknowledgements

- VAERS (CDC and FDA teams)
- CISA Project and Investigators
- COVID-19 Vaccine Task Force
- COVID-19 Vaccine Task Force, Vaccine Safety Team
- Immunization Safety Office

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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.



April 23, 2021 ACIP meeting to discuss Janssen COVID-19 Vaccine

- Additions to

CDC interim clinical considerations

“all women aged <50 years should be aware of the rare risk of TTS after receipt of the Janssen COVID-19 Vaccine and the availability of other [...] vaccines [...] for which this risk has not been seen.”

FDA EUA fact sheet for vaccination providers (below) and patients

“Reports [...] suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites [...] combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination. The reporting rate of thrombosis with thrombocytopenia following administration of the Janssen COVID-19 Vaccine has been highest in females ages 18 through 49 years; some cases have been fatal.”

<https://www.cdc.gov/vaccines/covid-19/info-by-product/janssen/risk-benefit-analysis.html>

<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>

<https://www.fda.gov/media/146304/download>

Locations of thromboses in U.S. TTS cases following Janssen COVID-19 vaccination by Aug 31, 2021, N=54 (not mutually exclusive)

Venous (n=49)

- Cerebral venous sinuses* (n=29)
- Abdominal (n=16)
- Extremity DVT (n=20)
- Pulmonary embolism (n=22)
- Internal jugular vein (n=13)
- Superficial extremity (n=3)

Arterial (n=9)

- Intracerebral (n=2)
- Abdominal (n=2)
- Extremity (n=3)
- Internal carotid (n=2)
- Aortoiliac (n=4)

- 1 case has only arterial thrombosis

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

Selected laboratory findings in U.S. TTS cases following Janssen COVID-19 vaccination by August 31, 2021, N=54

- **Platelet nadir levels (normal levels: 150,000–450,000 per microliter)***
 - <25,000 (n=21)
 - 25,000-<50,000..... (n=16)
 - 50–<100,000..... (n=11)
 - 100,000–149,000... (n=6)
- **Heparin-PF4 ELISA HIT antibody results**
 - Positive (+)..... (n=44)†
 - Negative (-)..... (n=3)
 - Not available..... (n=7)

* Platelet nadir range: 5,000-127,000 per microliter (median: 32,500)

† Tier 2 TTS required a positive (+) heparin-PF4 ELISA antibody test as part of definition

Treatment and outcomes among U.S. TTS cases following Janssen COVID-19 vaccination by Aug 31, 2021, N=54

■ Selected medical treatments

- Heparin (n=22)
 - 11/15 (73%) admitted before HAN*
 - 11/39 (28%) admitted after HAN*
- Non-heparin anticoagulants (n=48)
- Platelet transfusion (n=22)
- Intravenous immunoglobulin (n=36)
- Corticosteroids (n=24)
- Plasmapheresis (n=4)

■ Procedures (n=23)

- Thrombectomy (n=16)
- Drain/shunt placement (n=5)
- Craniectomy (n=7)
- Surgical resection (n=3)
- IVC filter placement (n=4)
- Large vessel stent (n=1)

SARS-CoV-2 testing results in U.S. TTS cases following Janssen COVID-19 vaccination as of Aug 31, 2021, N=54

■ SARS-CoV-2 nucleic acid or antigen viral assay

- Negative (n=45)*
- Positive (n=0)
- Not available (n=9)

■ SARS-CoV-2 serology by nucleocapsid antibody

- Negative (n=5)
- Positive (n=2)**
- Not available/not specified (n=47)†

* One patient had a positive antigen test followed immediately by a negative nucleic acid test

** Neither of these patients reported a history of COVID-19.

† One had a negative serology, the report did not specify whether nucleocapsid or spike protein antibody

TTS Death reporting rate after Janssen COVID-19 Vaccine (N=10 confirmed or suspicious deaths)

Overall death reporting rate: 0.71 per million Janssen COVID-19 Vaccine doses

| Age group | Females | | | Males | | |
|---------------|------------|------------------|---|------------|------------------|---|
| | TTS deaths | Doses admin | Reporting rate [†] (per million) | TTS deaths | Doses admin | Reporting rate [†] (per million) |
| 18-29 yrs old | 0 | 1,089,649 | 0 | 1 | 1,565,212 | 0.64 |
| 30-39 yrs old | 2 | 1,037,386 | 1.93 | 0 | 1,443,900 | 0 |
| 40-49 yrs old | 2 | 1,108,495 | 1.80 | 2 | 1,392,990 | 1.44 |
| 50-64 yrs old | 3 | 2,002,984 | 1.50 | 0 | 2,338,263 | 0 |
| 65+ yrs old | 0 | 1,096,923 | 0 | 0 | 1,004,285 | 0 |
| Total | 7 | 6,335,437 | 1.10 | 3 | 7,744,650 | 0.39 |

*Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>; [†] Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

Vaccination through August 31, 2021