

Updates on Thrombosis with Thrombocytopenia Syndrome (TTS)

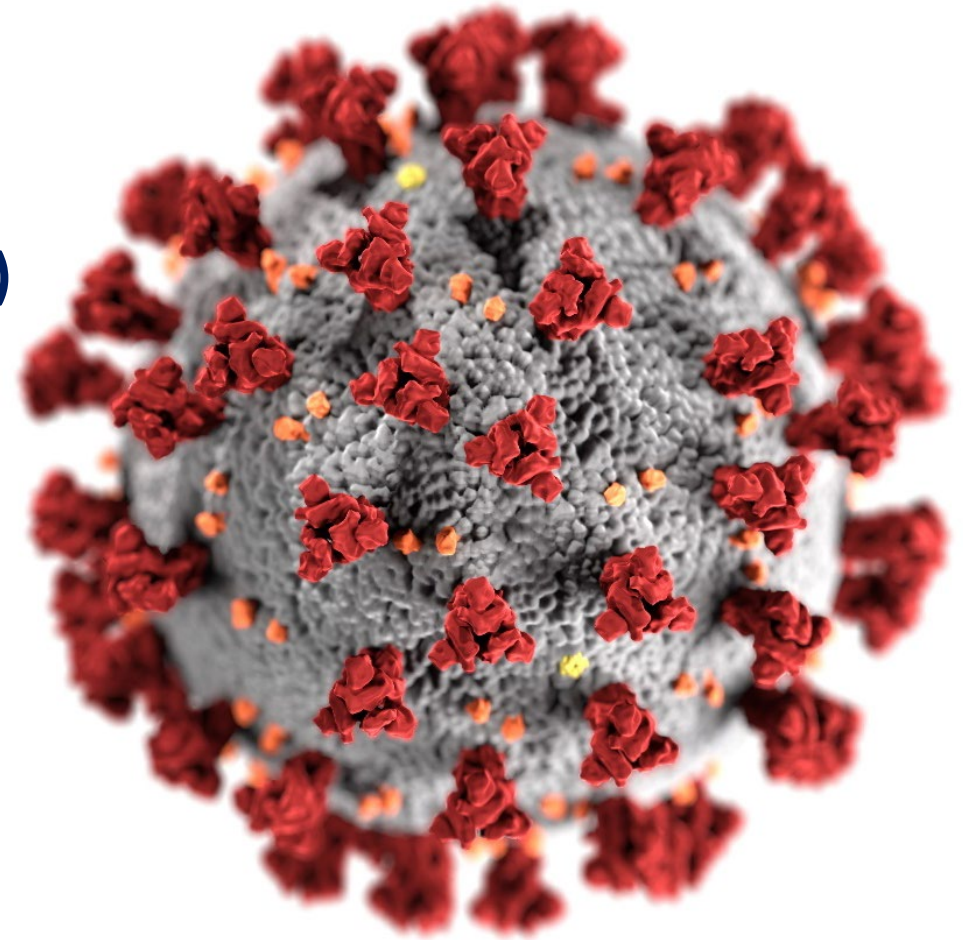
Advisory Committee on Immunization Practices (ACIP)

Dec 16, 2021

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Vaccine Safety Team

CDC COVID-19 Vaccine Task Force



cdc.gov/coronavirus



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 replacement therapy or birth control pills, pregnancy, cancer, older age
- 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



* Source: <https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis>

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 (μL)
- Platelets stop bleeding by clumping and forming plugs in blood vessel injuries
- Thrombocytopenia is a condition in which a person has a low blood platelet count ($<150,000$ per μL)
- Dangerous internal bleeding can occur when the platelet count falls below 10,000 per μL
- 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>

Thrombosis with thrombocytopenia syndrome (TTS): new syndrome recognized after adenoviral-vectored COVID-19 vaccines



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

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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 should be listed as very rare side effects of Vaxzevria (formerly AZD1225A) COVID-19 vaccine.
In reaching its conclusion, the committee took into account the latest data and advice from an ad hoc expert group.

Research

JAMA | Original Investigation

US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination: March 2 to April 21, 2021

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Morbidity and Mortality Weekly Report

Early Release / Vol. 70

April 30, 2021

Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19 Vaccine — United States, March–April 2021

David K. Shay, MD¹; Julianne Gee, MPH¹; John R. Su, MD, PhD¹; Tanya R. Myers, PhD¹; Paige Marquez, MSPH¹; Ruiling Liu, PhD¹; Bicheng Zhang, MS¹; Charles Licata, PhD¹; Thomas A. Clark, MD¹; Tom T. Shimabukuro, MD¹

On February 27, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Janssen (Ad.26.COV2.S) COVID-19 vaccine (Janssen Biotech, Inc., a Janssen Pharmaceutical company, Johnson

VAERS reports reviewed, 97% were classified as nonserious and 3% as serious,[†] including three reports among women of cases of thrombosis in large arteries or veins accompanied by thrombocytopenia during the second week after vaccination.

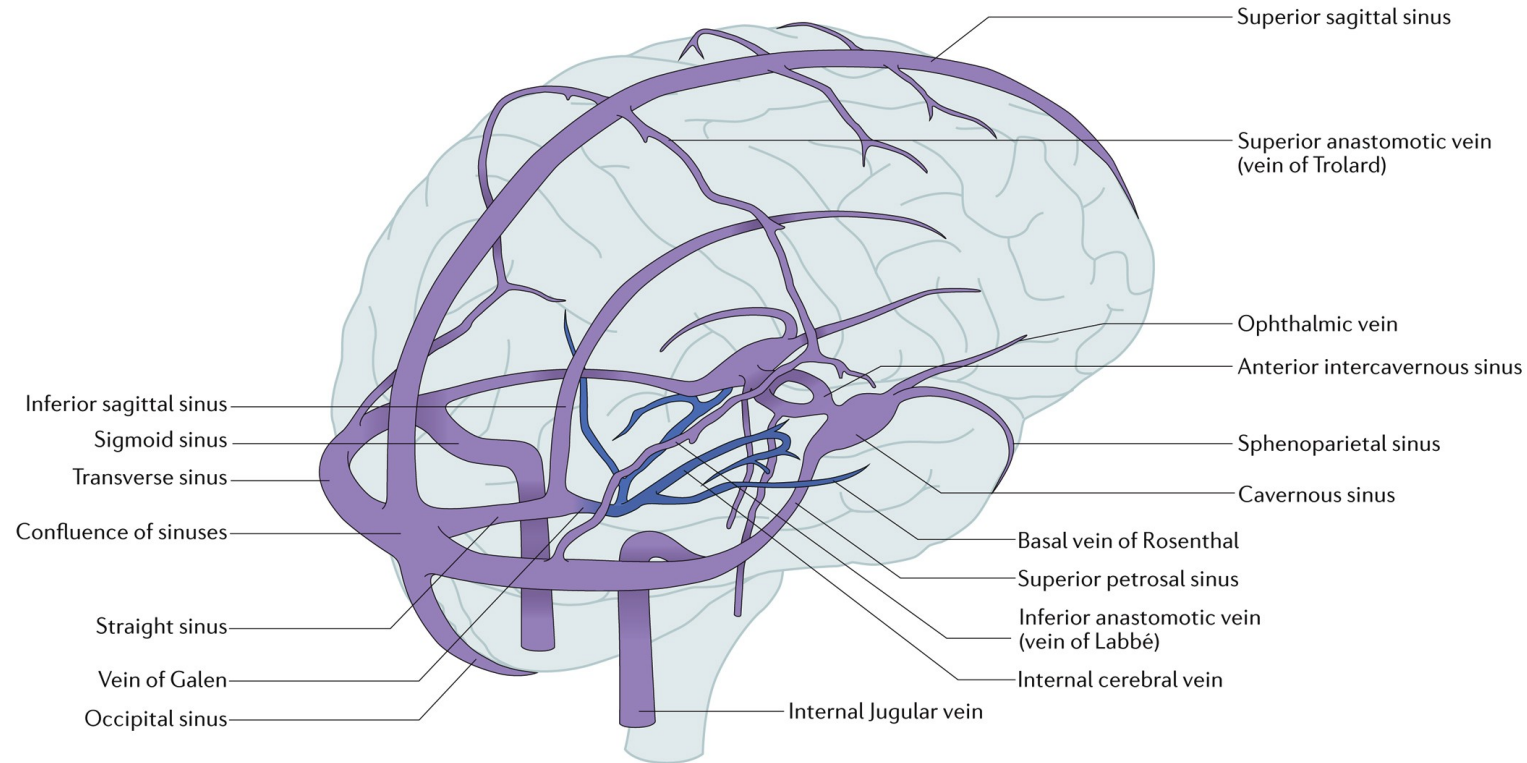


<https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>

<https://jamanetwork.com/journals/jama/fullarticle/2779731>

https://www.cdc.gov/mmwr/volumes/70/wr/mm7018e2.htm?s_cid=mm7018e2_w

Cerebral Venous Sinus Thrombosis (CVST)



Nature Reviews | Neurology



Source: Silvis SM et al, Nature Reviews Neurology **13**, 555-565 (2017).

Features of severe CVST

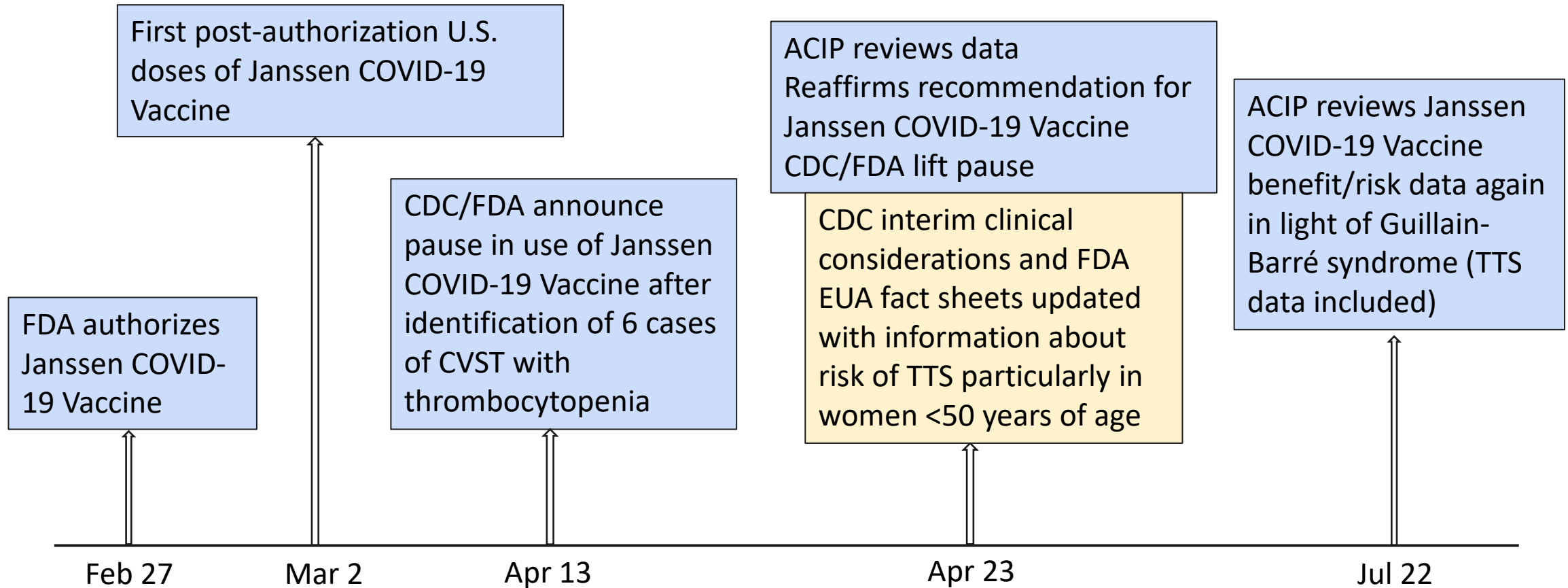
- CVST is often under-diagnosed due to its nonspecific presentation
- Short-term death from CVST usually caused by brain herniation
 - Resulting from large or multiple hemorrhages (bleed) or from diffuse brain edema (swelling)
- Reported prognostic factors for poor short-term outcome include:
 - Anatomical: brain herniation, hemorrhage
 - Clinical presentation: seizures, depressed consciousness, altered mental status



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



<https://www.cdc.gov/media/releases/2021/s0413-JJ-vaccine.html>; <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>;
<https://www.fda.gov/media/146304/download>; <https://www.cdc.gov/mmwr/volumes/70/wr/mm7032e4.htm>

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



VAERS

Vaccine Adverse Event Reporting System

<http://vaers.hhs.gov>

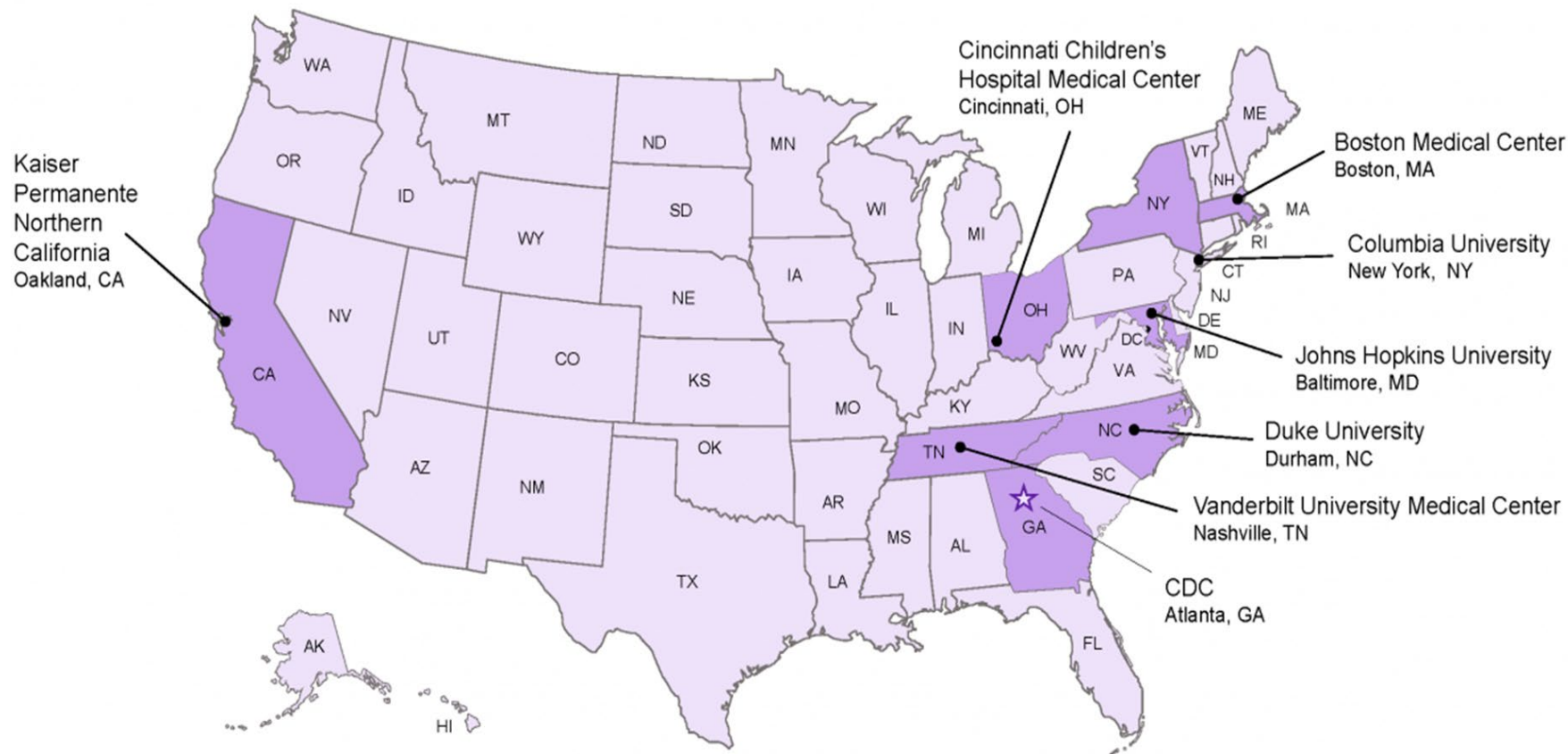




CISA

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 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
- 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, abdominal venous or arterial thrombosis	<150,000 cells/ μ L	No
Tier 2	Only in 'typical' location(s), e.g., pulmonary embolism, deep vein thrombosis of extremity	<150,000 cells/ μ L	Yes

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



*PF4 ELISA: platelet factor 4 enzyme-linked immunosorbent assay

Analytic periods

- Descriptive epidemiology and reporting rates for TTS cases receiving Janssen COVID-19 Vaccine March 2–August 31, 2021
- Summarize information about all deaths among TTS cases following Janssen COVID-19 Vaccine confirmed by December 9, 2021
- Reporting rates for TTS deaths receiving Janssen COVID-19 Vaccine March 2–August 31, 2021



Epidemiology of U.S. TTS cases following Janssen COVID-19 vaccination (March 2–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)
- Female (n=37), male (n=17)
- 26 (48%) are women aged <50 years
- 83% in white non-Hispanic persons
- 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



*Vaccinated March 2–August 31, 2021

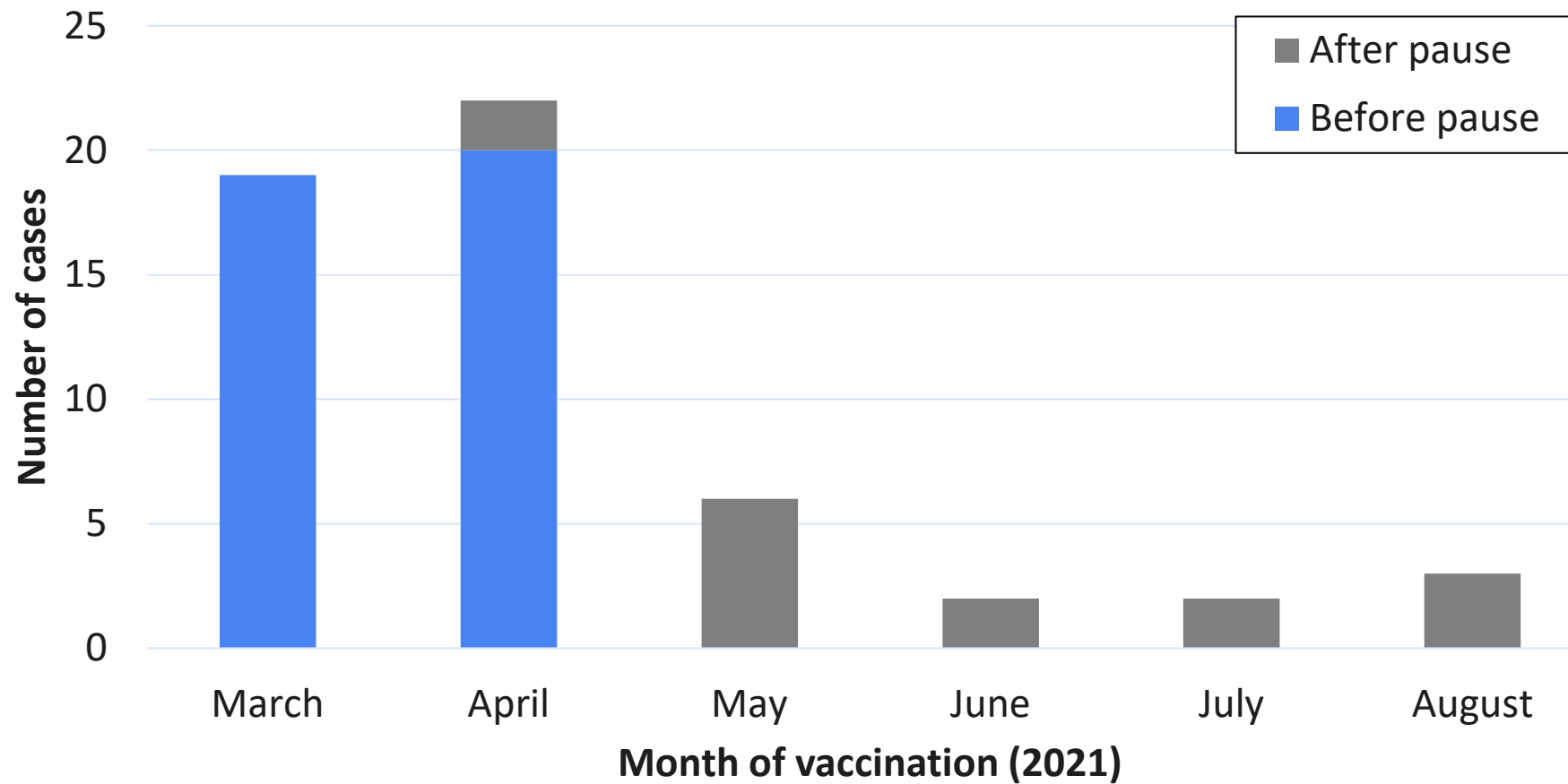
Characteristics of U.S. TTS cases after Janssen COVID-19 vaccination*, N=54 (continued)

- 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 (i.e., none after booster doses)



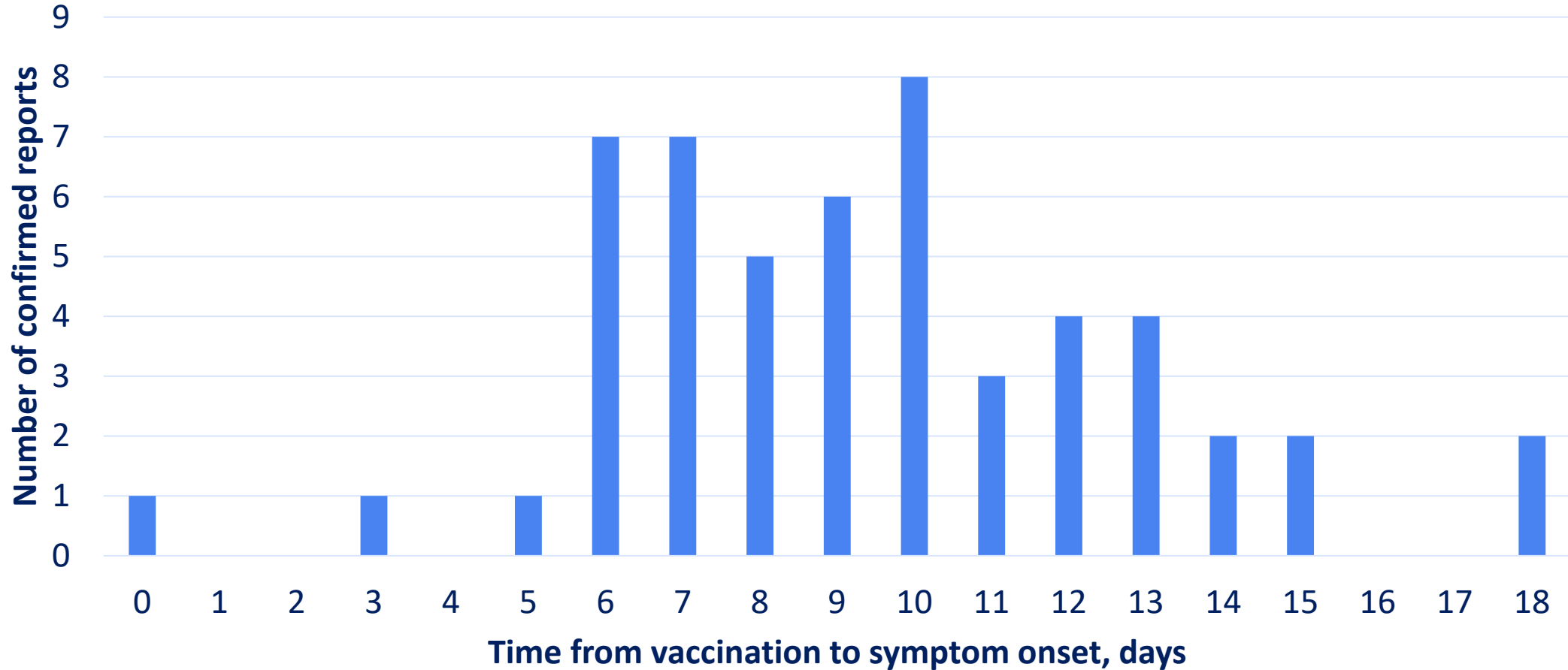
*Vaccinated March 2–August 31, 2021

Number of TTS cases following Janssen COVID-19 vaccination, by month of vaccination* (N=54)



*Vaccinated March 2–August 31, 2021

U.S. TTS cases, by 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. Vaccinations March 2–August 31, 2021

Venous thrombosis risk factors in U.S. TTS cases following Janssen COVID-19 vaccination*, N=54

Risk factor** (not mutually exclusive)	n (%)
Obesity	25 (46)
Hypertension	16 (30)
Diabetes	7 (13)
Systemic estrogen therapy [†]	3 (6)
Other venous thrombosis risk factor [‡]	3 (6)
None of the above risk factors	21 (39)

* Vaccinated March 2–August 31, 2021

** Venous thrombosis risk factors as described in Lijfering WM et al, Br J Haematol 2020; and Crous-Bou M et al, Semin Thromb Hemost 2016.

[†] 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 surviving hospitalization
 - Median 9 days
 - Range: 1–132 days
 - Interquartile range: 6–17 days
- Outcome of hospitalization
 - Death (n=8)
 - Discharged to post-acute care facility (n=9)
 - Discharged home (n=37)



*Vaccinated March 2–August 31, 2021

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



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50-64 yrs old	9	2,002,984	4.49	5	2,338,263	2.14
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Highest rates

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Reporting rates of TTS after Janssen COVID-19 vaccine, vaccination March 2–August 31, 2021 (N=54)

14.1 million total Janssen COVID-19 vaccine doses administered*

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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

Similar rates

Overall reporting rate: 3.83 cases per million Janssen



*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: data presented to ACIP Jul 2021 vs Dec 2021

Age group	Females (Jul ACIP*)			Females (Dec ACIP**)		
	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: data presented to ACIP Jul 2021 vs Dec 2021

Age group	Males (Jul ACIP*)			Males (Dec ACIP**)		
	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

U.S. TTS deaths following Janssen COVID-19 vaccination



Epidemiology of TTS deaths following Janssen COVID-19 vaccination through December 9, 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 COVID-19 vaccination through December 9, 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
- 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 2021

Date of meeting	Purpose of discussion	Cut-off for data	No. Janssen doses given	Total TTS cases	Total 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 Guillain-Barré)	Jul 8	12.5 million	38	4

Revisit TTS updates to ACIP 2021: comparing previously presented data with data as of Dec 9, 2021

Date of meeting	Purpose of discussion	Cut-off for data	No. Janssen doses given	Total TTS cases	Total 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 Guillain-Barré)	Jul 8	12.5 million	38 50	4 6
Dec 16	TTS update	Aug 31	14.1 million	54	8



TTS death reporting rate with Janssen COVID-19 vaccination 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



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

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50-64 yrs old	2	2,002,984	1.00	0	2,338,263	0
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Highest rates



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

% of TTS cases with death: Vaccinated before pause^{**}: 5/39 (13%)

Vaccinated after pause^{**}: 3/15 (20%)



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

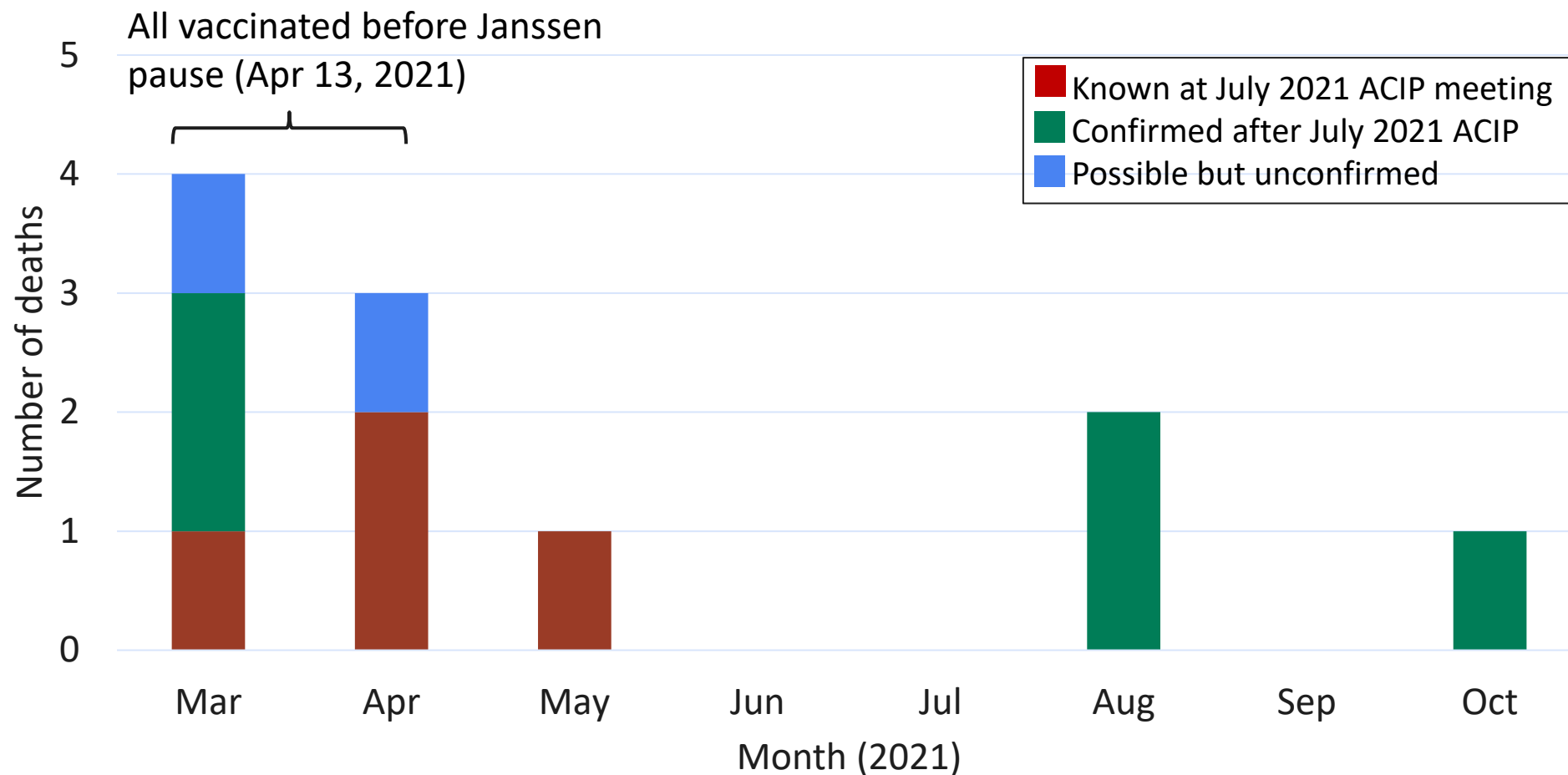
In addition: two possible TTS deaths with Janssen COVID-19 vaccination*

- Features shared with confirmed TTS deaths after Janssen COVID-19 vaccine
 - 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 hemorrhage



*Of these two possible TTS deaths following Janssen COVID-19 vaccination, one is in a woman between 50–64 years of age and the other in a man 40–49 years. Both vaccinated before the pause in Janssen COVID-19 vaccination.

Confirmed and possible TTS deaths following Janssen COVID-19 Vaccine, by month of vaccination as of Dec 9, 2021*



*8 TTS deaths confirmed in persons with Janssen COVID-19 vaccination by August 31, 2021; 1 TTS death confirmed with Janssen COVID-19 vaccination after August 31, 2021



Limitations

- Possible underdiagnosis of CVST and TTS
- VAERS is passive surveillance system
- Therefore, case and death reporting rates might be underestimates



Summary

- U.S. TTS case reporting rate (3.8 per million doses) following Janssen COVID-19 vaccination higher than previously presented
 - Case reporting rates for men 40–49 years and women 50–64 years similar to women 18–29 years (~4–5 per million doses)
- 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)
 - Proportion of TTS cases with death did not decrease after Janssen pause on April 13

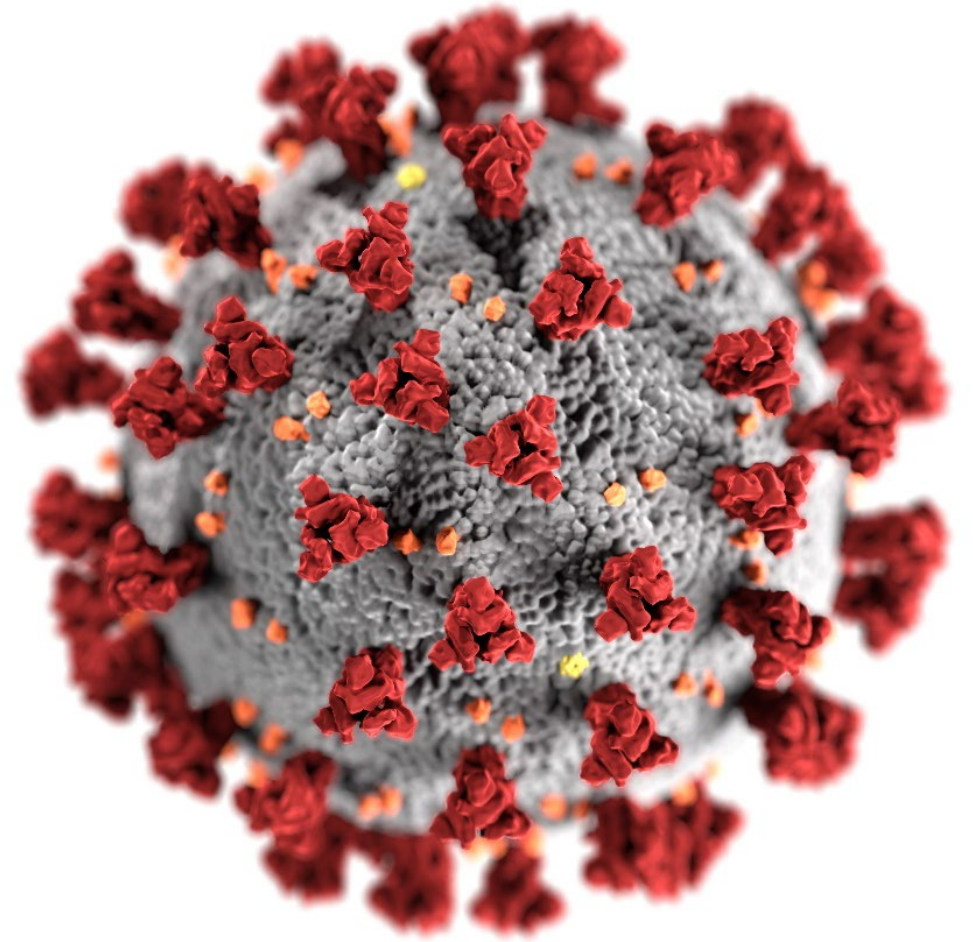


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- VAERS (CDC and FDA teams)
- CISA Project and Investigators
- COVID-19 Vaccine Task Force
- COVID-19 Vaccine Task Force, Vaccine Safety Team
- Immunization Safety Office
- People reporting to VAERS



Thank you!



For more information, contact CDC
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TTY: 1-888-232-6348 www.cdc.gov

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