

Updates on Thrombosis with Thrombocytopenia Syndrome (TTS)

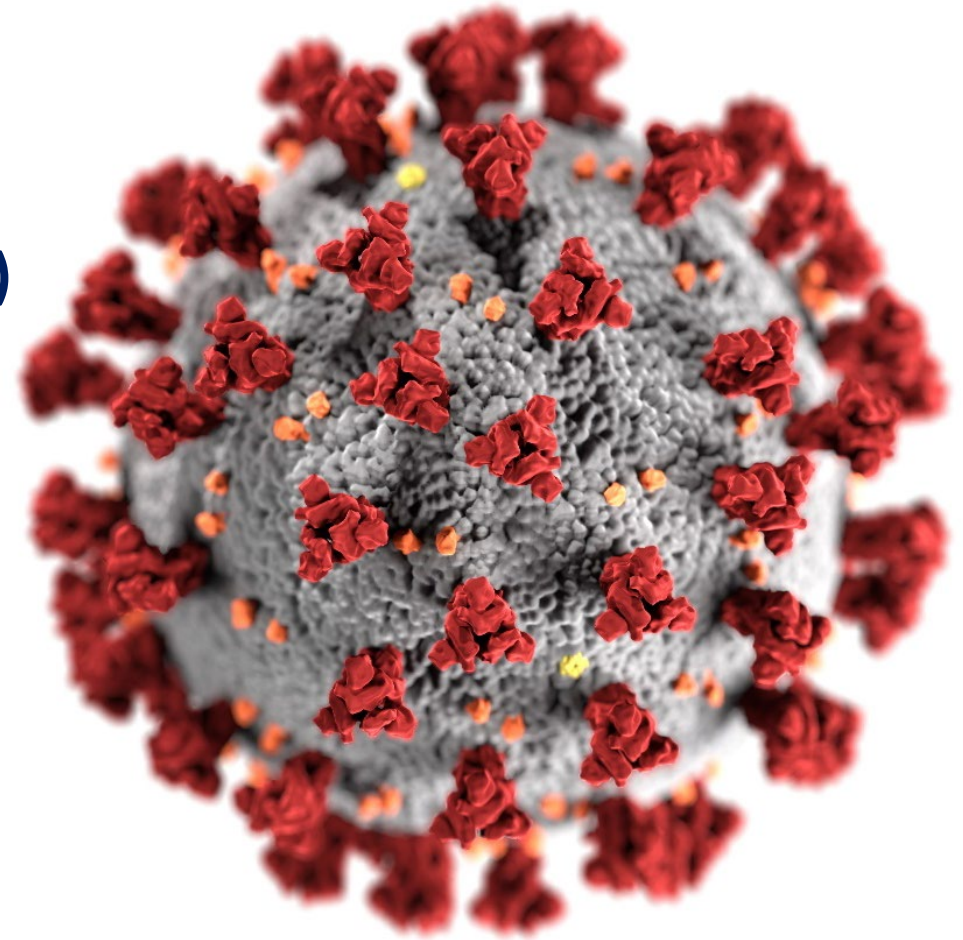
Advisory Committee on Immunization Practices (ACIP)

Dec 16, 2021

Isaac See, MD

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



Medicines Human regulatory Veterinary regulatory Committees News & events Partners & networks About us

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

Share

News 07/04/2021

EMA confirms overall benefit-risk remains positive

EMA's safety committee (PRAC) has concluded today that the very rare cases of unusual blood clots should be listed as very rare side effects of Vaxzevria (formulation with adjuvant).

In reaching its conclusion, the committee took into account the advice from an ad hoc expert group.

Research

JAMA | Original Investigation

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

Isaac See, MD; John R. Su, MD, PhD, MPH; Allison Lale, MD, MPH; Emily Jane Woo, MD, MPH; Alice Y. Guh, MD, MPH; Tom T. Shimabukuro, MD, MPH, MBA; Michael B. Streiff, MD; Agam K. Rao, MD; Allison P. Wheeler, MD, MSCI; Suzanne F. Beavers, MD; Anna P. Durbin, MD; Kathryn Edwards, MD; Elaine Miller, RN, MPH; Theresa A. Harrington, MD, MPH&TM; Adamma Mba-Jonas, MD, MPH; Narayan N. Duong T. Nguyen, DO; Kawsar R. Talaat, MD; Victor C. Urrutia, MD; Shannon C. Walker, MD; C. Buddy Creech, MD; Thomas A. Clark, MD, MPH; Frank DeStefano, MD, MPH; Karen R. Broder, MD

Centers for Disease Control and Prevention

MMWR

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.COVS.2.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.

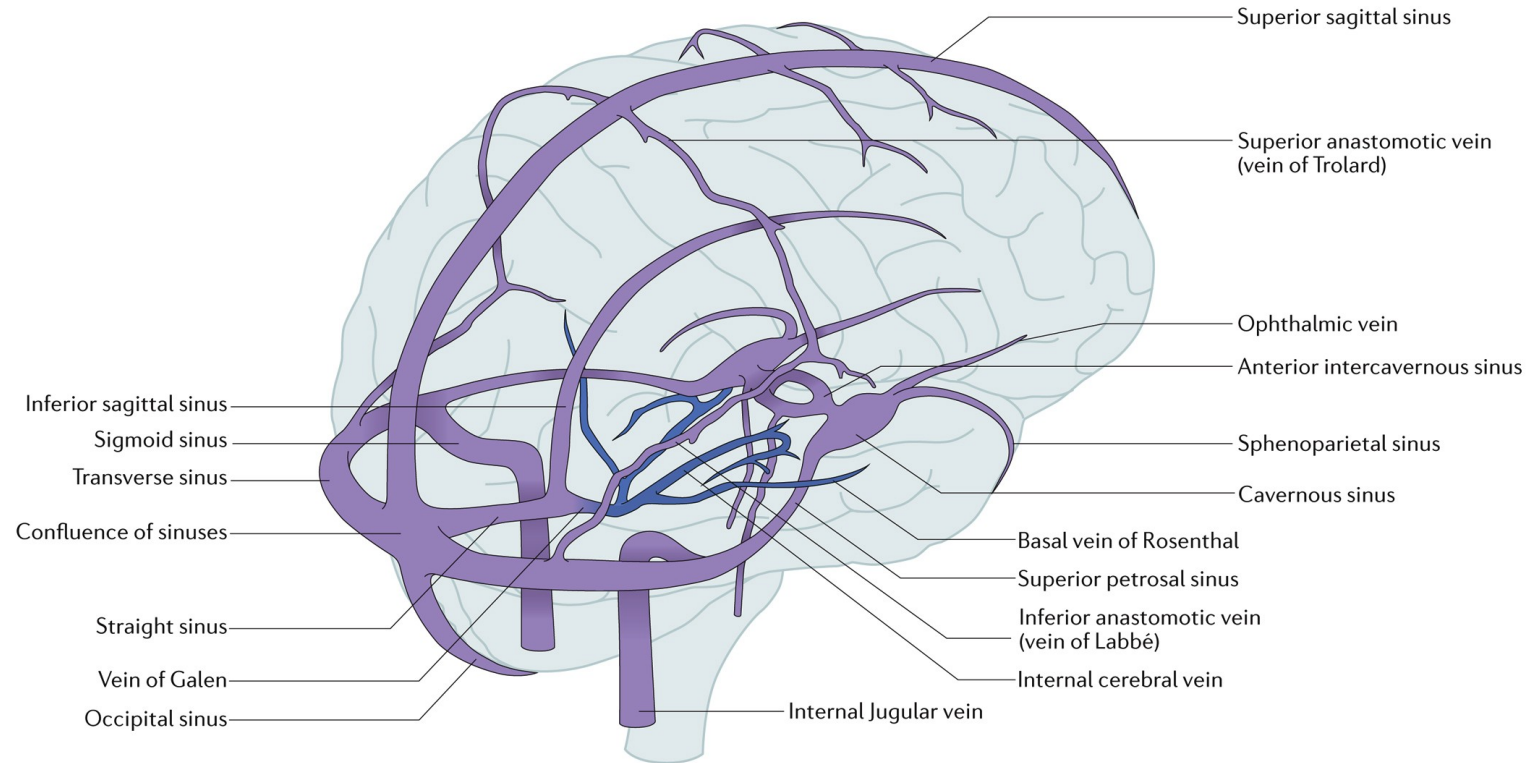
<https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>

<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

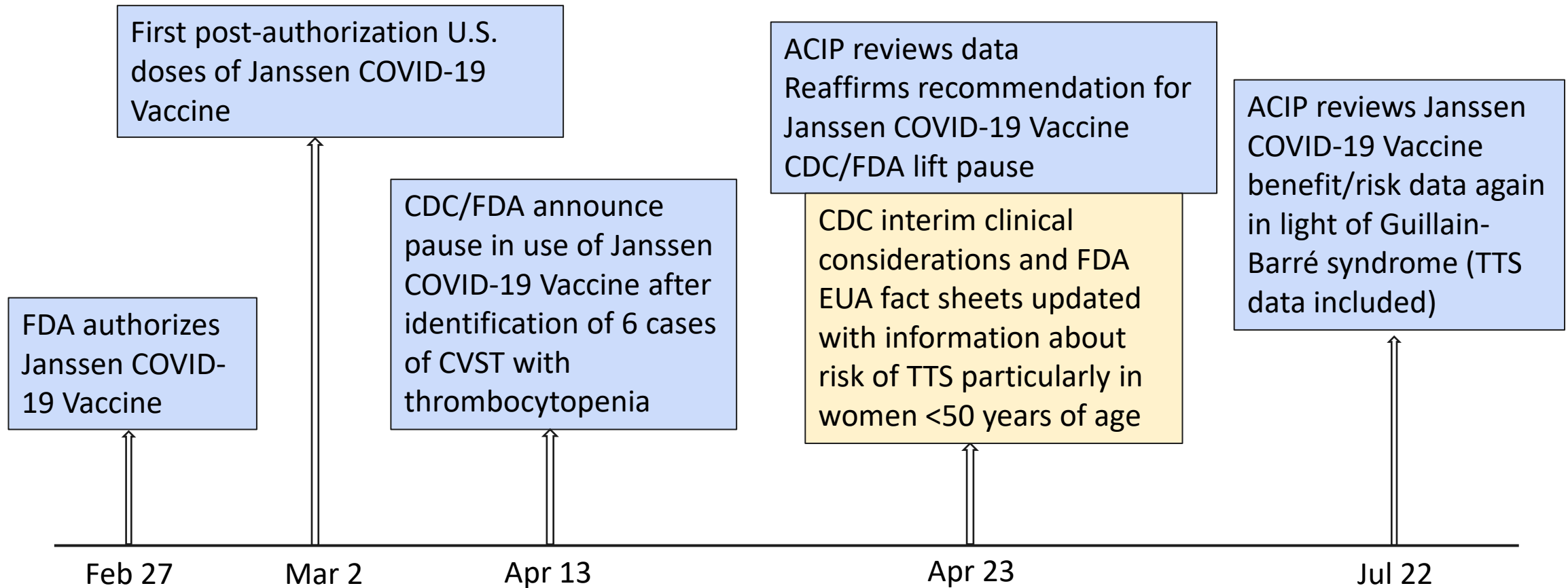
- CVST is often under-diagnosed due to its nonspecific presentation
- Short-term death from CVST usually caused by brain herniation
 - Resulting from large or multiple hemorrhages (bleed) or from diffuse brain edema (swelling)
- Reported prognostic factors for poor short-term outcome include:
 - Anatomical: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

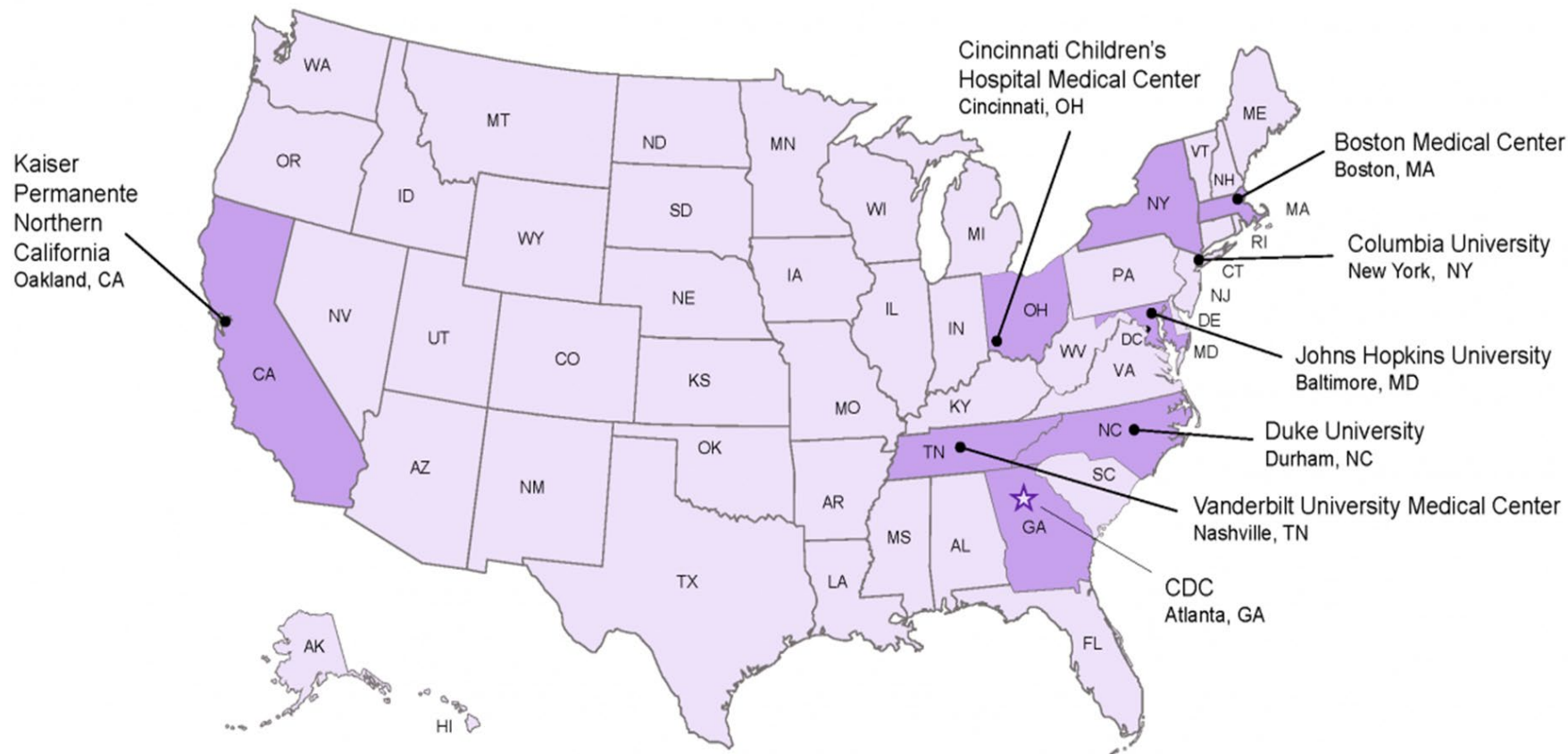




CISA

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

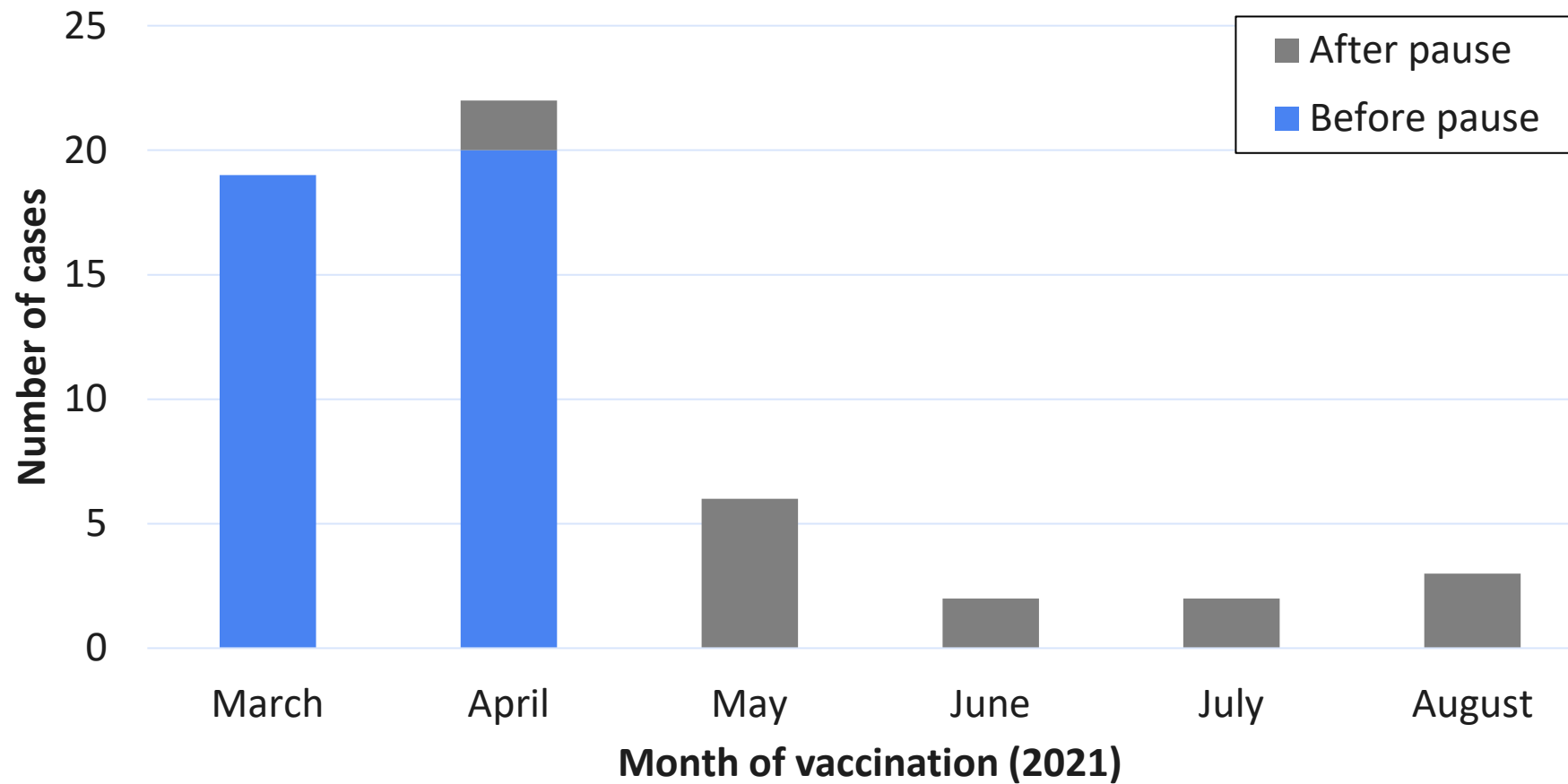
Characteristics of U.S. TTS cases after Janssen COVID-19 vaccination*, N=54 (continued)

- 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)



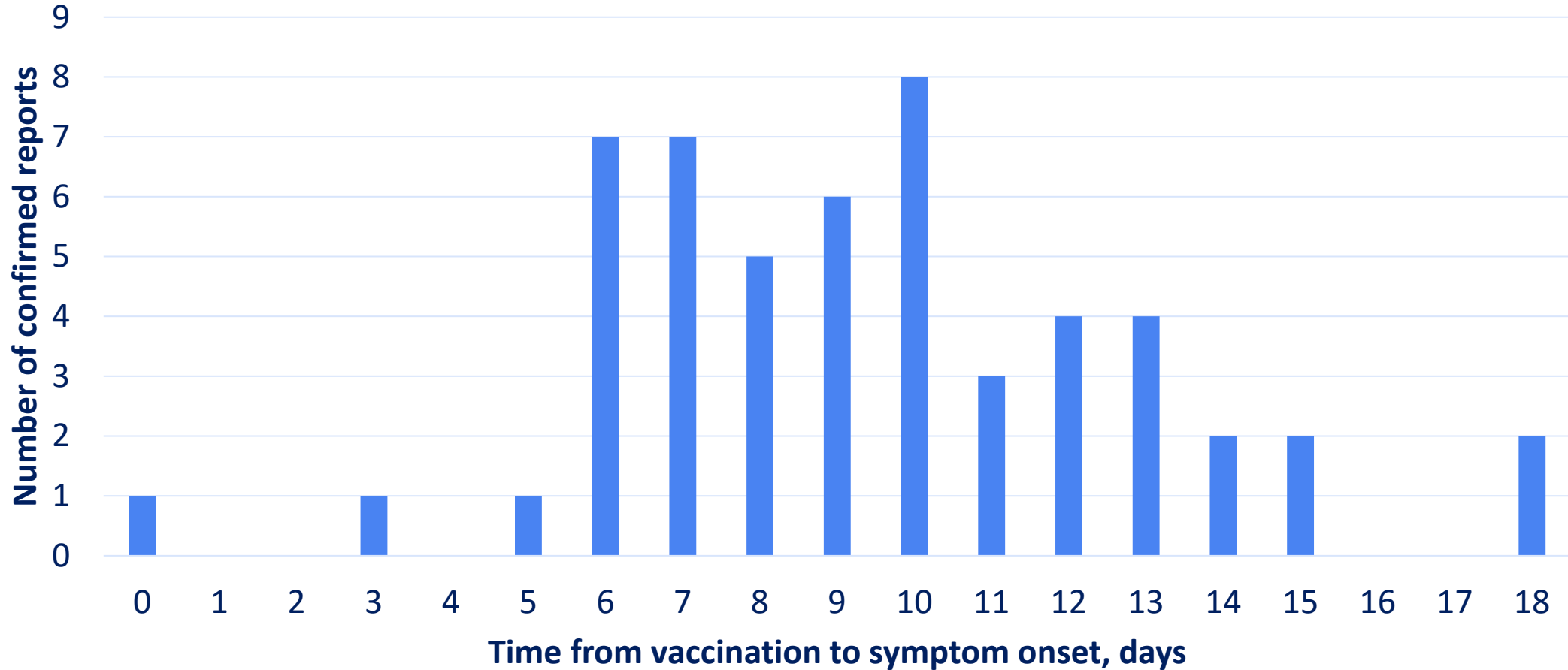
*Vaccinated March 2–August 31, 2021

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



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*

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

Highest rates

Overall reporting rate: 3.83 cases per million Janssen COVID-19 vaccine doses administered

*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, vaccination March 2–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

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

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

Highest rates



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 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

% 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

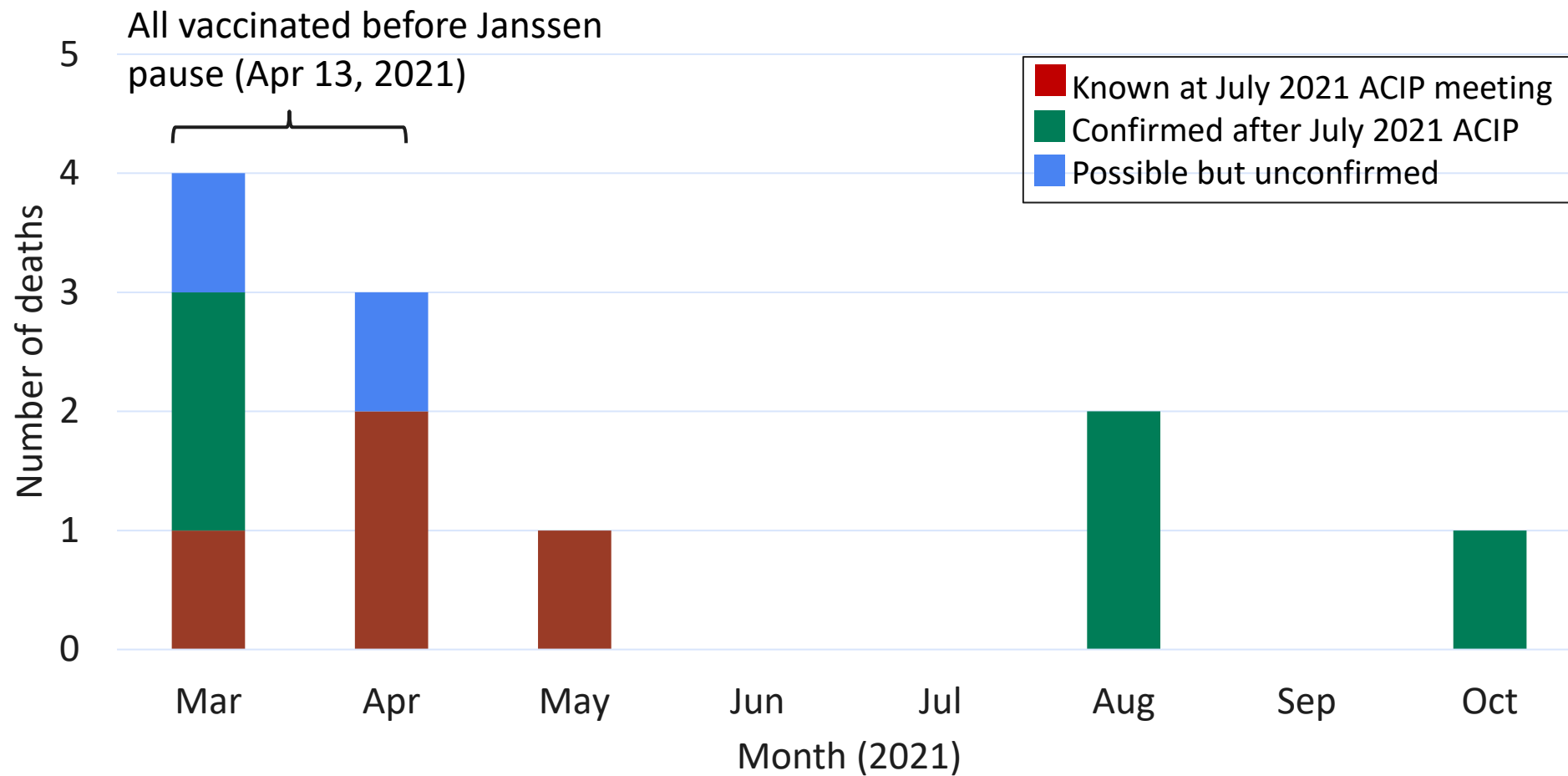
In addition: two possible TTS deaths with Janssen COVID-19 vaccination*

- 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

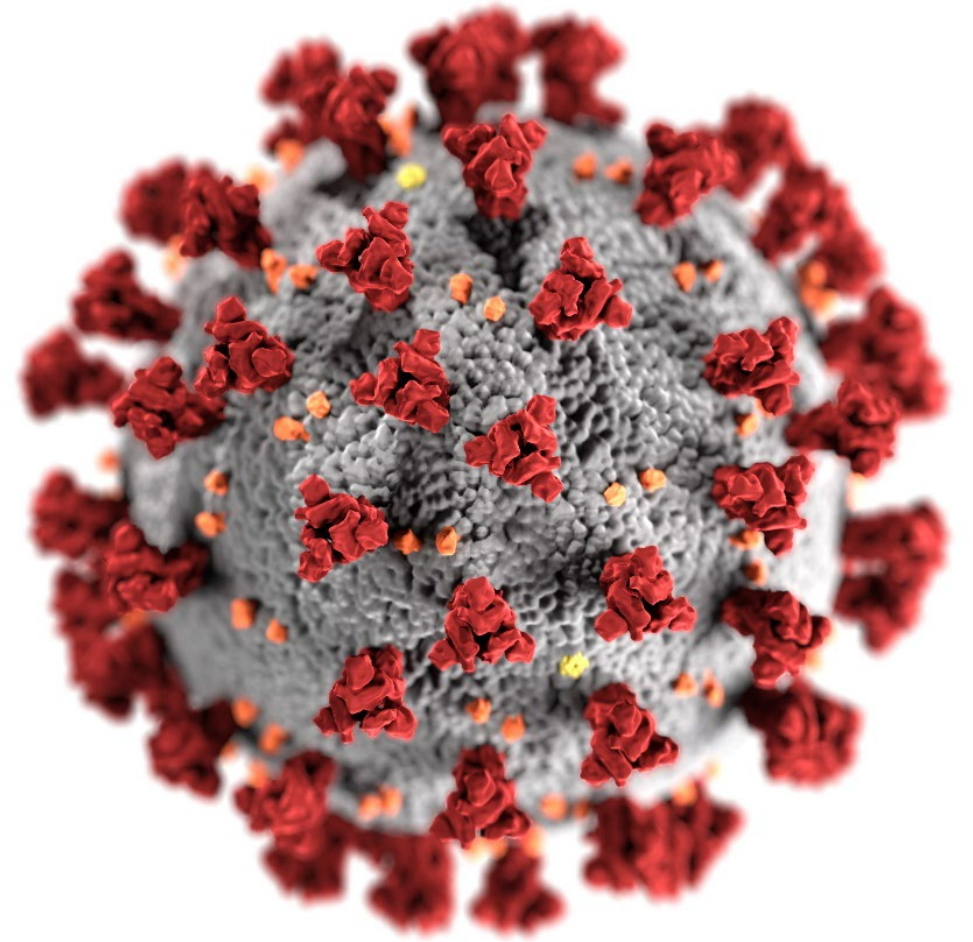


Acknowledgements

- 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
- People reporting to VAERS



Thank you!



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.

Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC or FDA.