Summary of Reports of Thrombosis and Thrombocytopenia Syndrome (TTS) in U.S. following vaccination with Janssen COVID-19 vaccine

Narayan Nair, MD
Division of Epidemiology
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
Food and Drug Administration

Disclaimer

My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate the US FDA.

Topics

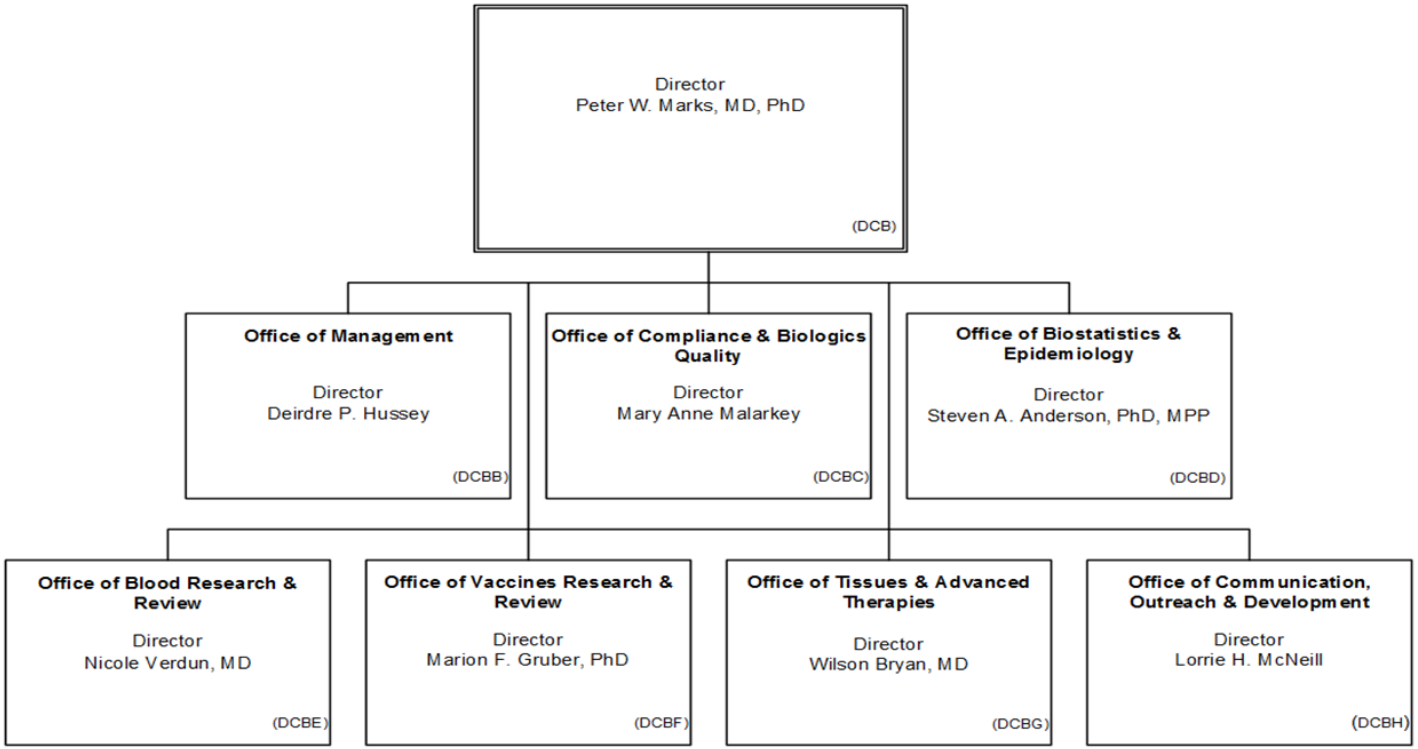
- Background
- Methods
- Summary of Cases

Background

Organization Chart

June 2020

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research



Timeline

- February 27, 2021 – U.S. FDA issues Emergency Use Authorization for Janssen COVID-19 vaccine
  - 1 case of CVST with thrombocytopenia observed in pre-authorization clinical trials in a 25-year-old male
- March 2, 2021 – Vaccination starts in U.S.
- March 19- April 12 – 6 cases of CVST with thrombocytopenia observed in women aged 18–48 years in early post-authorization monitoring
- April 13 – FDA and CDC recommend pause as investigation into cases continues
  - Notification published provided additional information and recommendations concerning the identification and treatment of suspected cases of TTS after Janssen COVID-19 vaccine.
- April 23 –FDA and CDC review available data and recommendations of CDC's Advisory Committee on Immunization Practices (ACIP) and conclude the known and potential benefits of Janssen COVID-19 Vaccine outweigh its known and potential risks in individuals 18 years of age and older
  - Fact sheets for health care providers and vaccine recipients revised to include information about the risk of this syndrome

Methods

Vaccine Adverse Event Reporting System (VAERS)

- U.S. National passive safety surveillance program administered by FDA and CDC, established in 1990
- Collects data from reports of adverse events following vaccination
- Prior to 2021 received ~50,000 reports annually (10-15% of reports thought to be serious)
- Reports can be made online or on paper

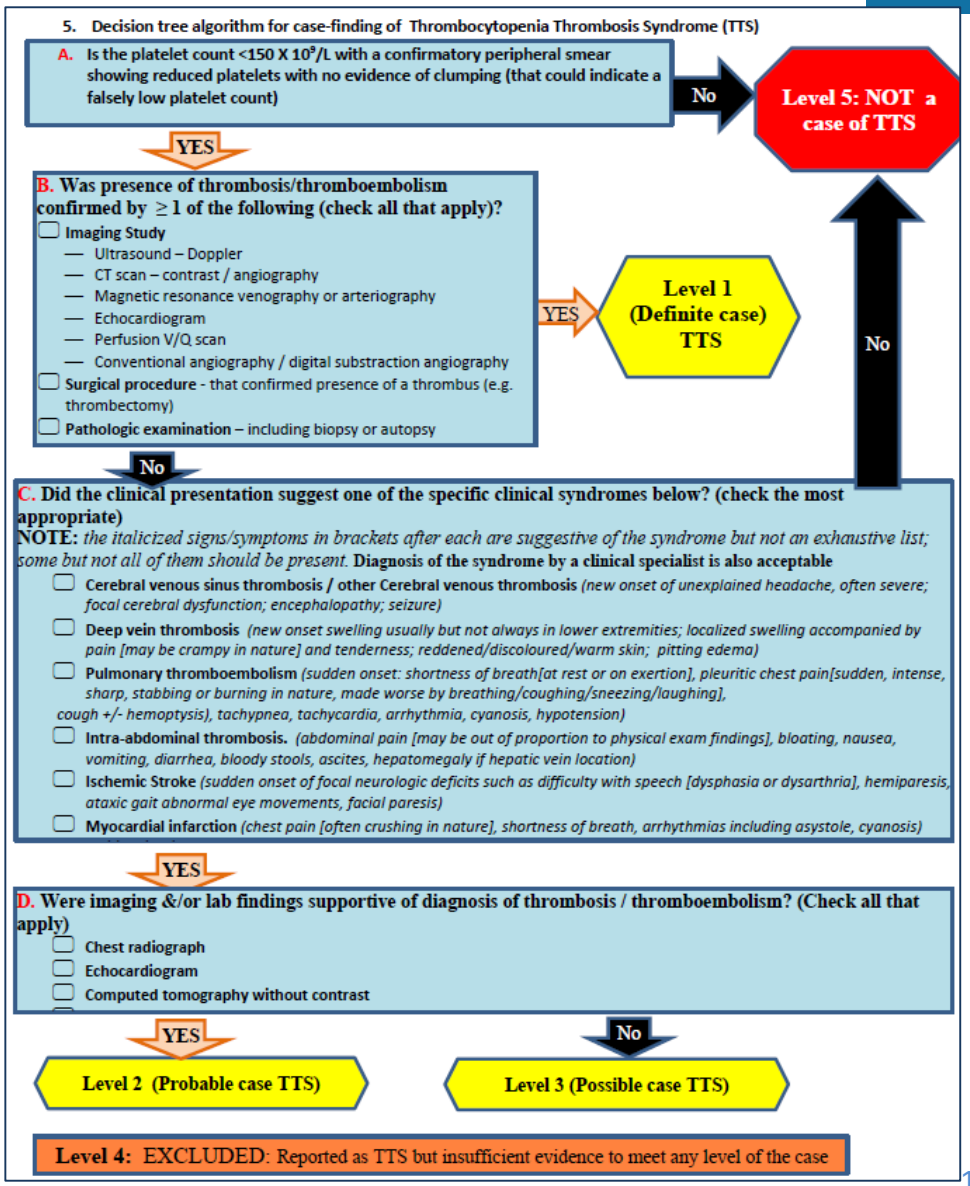
Evaluating TTS following Janssen COVID-19 vaccine

- FDA physicians review incoming VAERS reports daily to identify potential TTS cases
- Healthcare providers directly contact CDC with potential TTS cases
  - CDC initiates an investigation and facilitates submission of a VAERS report
- VAERS database search for possible TTS reports
  - Large vessel thrombosis and/or embolism (any report)
  - Did not include the more common thrombosis events*; these events will be evaluated in subsequent analysis
- Medical records are requested for all potential TTS cases to confirm thrombosis with laboratory evidence of thrombocytopenia

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

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

- Platelet count <150 X 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

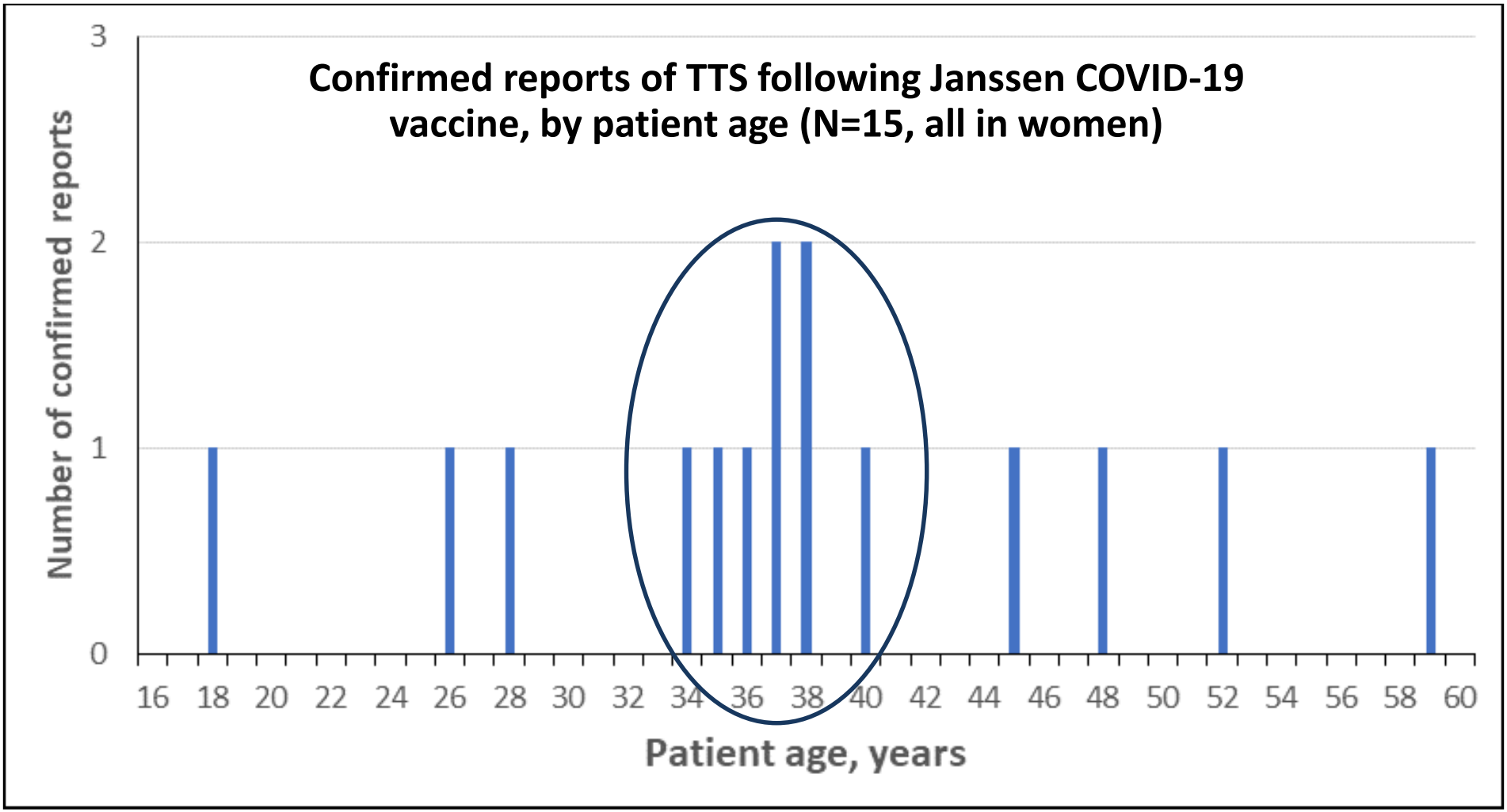
Summary of Cases

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

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

[*] Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; [†] One case in female aged <50 years 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)
Number of confirmed reports
0
1
2
3
16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60
Patient age, years

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

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

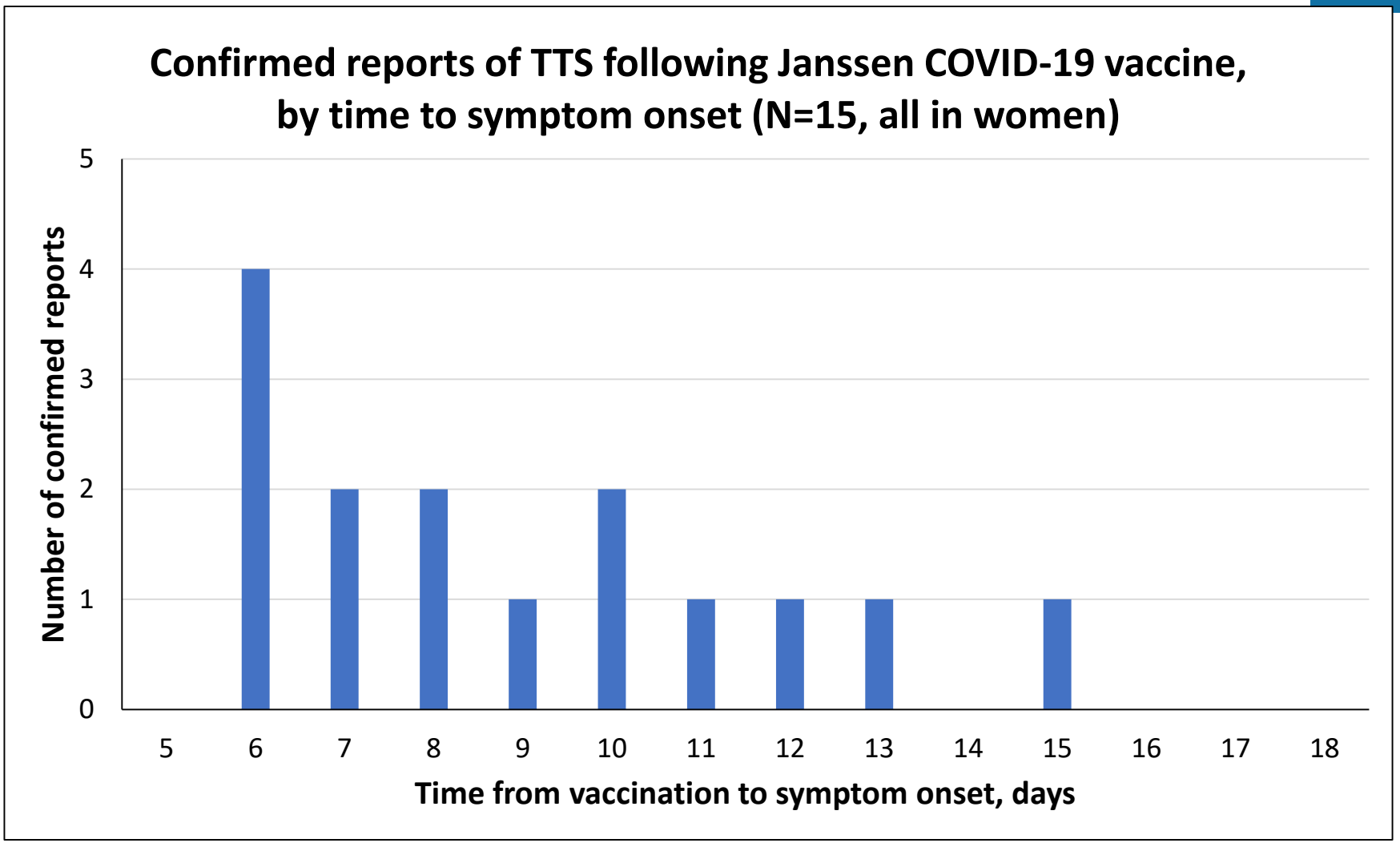
	Females		
Age group	**TTS cases**	**Doses admin**	**Reporting rate‡**
18-29 years old	**3**	579,709	5.2 per million
30-39 years old	**7**	594,215	11.8 per million
40-49 years old	**3**	692,370	4.3 per million
50-64 years old	**2**	1,367,529	1.5 per million
65+ years old	**0**	757,710	0 per million

* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; † One case in female aged <50 years 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

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
- 5 cases admitted after health alert notification (HAN) on April 13, 2021
- 12 cases were cerebral venous sinus thrombosis (CVST)
- Pregnant or post-partum* (n=0)
- History of COVID-19 (n=2)
- Risk factors for thrombosis†
  - 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; † Reference source: https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis


Confirmed reports of TTS following Janssen COVID-19 vaccine, by time to symptom onset (N=15, all in women)
Number of confirmed reports
0
1
2
3
4
5
5
6
7
8
9
10
11
12
13
14
15
16
17
18
Time from vaccination to symptom onset, days

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 vein

- **Other locations (n=10)**
  - Portal vein†
  - Hepatic vein
  - Superior mesenteric artery†
  - Splenic artery†
  - Pulmonary artery
  - Lower extremity vein†
  - Internal jugular vein
  - Carotid artery
  - Brachial vein†
  - Femoral vein and artery†
  - Iliac artery†

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

† patients without CVST had thrombosis in these locations

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

- **Initial†**
  - Headache (all started ≥6 days after vaccination)
  - Chills
  - Fever
  - Nausea/vomiting
  - Malaise/lethargy
  - Abdominal pain

- **Later in clinical course†**
  - Headache (including severe)
  - Unilateral weakness
  - Speech difficulty
  - Dizziness

* Information for one patient with cerebral venous sinus thrombosis is undergoing review

† Occurring in ≥2 patients

Selected laboratory findings in TTS patients, N=15

- **Platelet levels (normal levels: 150,000–450,000 per mm^3)***
  - <50,000……. (n=10)
  - 50–<100,000……. (n=3)
  - 100,000–149,000…(n=2)

- **PF4 HIT† 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)
  - Nonheparin anticoagulants (n=12)
  - Platelet transfusion (n=7)
  - Intravenous immunoglobulin (n=8)

- **Outcomes†**
  - Death (n=3)§
  - Remain hospitalized (n=7)
    - Intensive care unit (n=4)
  - Discharged home (n=5)

* Based on 14 patients
† As of April 21, 2021
§ None of the patients who died received heparin

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
- Safety surveillance and research on TTS continues

Acknowledgments

FDA Division of Epidemiology

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