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.”

- 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

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

- Feb 27: FDA authorizes Janssen COVID-19 Vaccine
- Mar 2: First post-authorization U.S. doses of Janssen COVID-19 Vaccine
- Apr 13: CDC/FDA announce pause in use of Janssen COVID-19 Vaccine after identification of 6 cases of CVST with thrombocytopenia
- Apr 23: 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

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

- **Feb 27**: FDA authorizes Janssen COVID-19 Vaccine
- **Mar 2**: CDC/FDA announce pause in use of Janssen COVID-19 Vaccine after identification of 6 cases of CVST with thrombocytopenia
- **Apr 13**: ACIP reviews data, reaffirms recommendation for Janssen COVID-19 Vaccine
- **Apr 23**: CDC interim clinical considerations and FDA EUA fact sheets updated with information about risk of TTS particularly in women <50 years of age

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

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

<table>
<thead>
<tr>
<th>TTS category</th>
<th>Thrombosis location</th>
<th>Platelet count</th>
<th>Positive PF4 ELISA test required?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 1</td>
<td>Unusual location, e.g., CVST, splanchnic venous or arterial thrombosis</td>
<td>&lt;150K cells/µL</td>
<td>No</td>
</tr>
<tr>
<td>Tier 2</td>
<td>Only in ‘typical’ location(s), e.g., pulmonary embolism, deep vein thrombosis of extremity</td>
<td>&lt;150K cells/µL</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- 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)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>n  (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>25 (46)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (30)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Systemic estrogen therapy*</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Other venous thrombosis risk factor**</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

*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*  

<table>
<thead>
<tr>
<th>Age group</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TTS cases</td>
<td>Doses admin</td>
</tr>
<tr>
<td>18-29 yrs old</td>
<td>5</td>
<td>1,089,649</td>
</tr>
<tr>
<td>30-39 yrs old</td>
<td>11</td>
<td>1,037,386</td>
</tr>
<tr>
<td>40-49 yrs old</td>
<td>10</td>
<td>1,108,495</td>
</tr>
<tr>
<td>50-64 yrs old</td>
<td>9</td>
<td>2,002,984</td>
</tr>
<tr>
<td>65+ yrs old</td>
<td>2</td>
<td>1,096,923</td>
</tr>
</tbody>
</table>

Overall reporting rate: 3.83 cases per million Janssen doses

* Source of doses administered: [https://covid.cdc.gov/covid-data-tracker/#vaccinations](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

<table>
<thead>
<tr>
<th>Age group</th>
<th>TTS cases</th>
<th>Doses admin</th>
<th>Reporting rate† (per million)</th>
<th>TTS cases</th>
<th>Doses admin</th>
<th>Reporting rate† (per million)</th>
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</thead>
<tbody>
<tr>
<td>18-29 yrs old</td>
<td>4</td>
<td>946,358</td>
<td>4.22</td>
<td>5</td>
<td>1,089,649</td>
<td>4.59</td>
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<tr>
<td>30-49 yrs old</td>
<td>17</td>
<td>1,934,574</td>
<td>8.79</td>
<td>21</td>
<td>2,145,881</td>
<td>9.79</td>
</tr>
<tr>
<td>50-64 yrs old</td>
<td>7</td>
<td>1,865,372</td>
<td>3.75</td>
<td>9</td>
<td>2,002,984</td>
<td>4.49</td>
</tr>
<tr>
<td>65+ yrs old</td>
<td>0</td>
<td>1,028,190</td>
<td>0</td>
<td>2</td>
<td>1,096,923</td>
<td>1.82</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>28</td>
<td>5,774,494</td>
<td>4.85</td>
<td>37</td>
<td>6,335,437</td>
<td>5.84</td>
</tr>
</tbody>
</table>

** Current data: vaccination through August 31, 2021
- Source of doses administered: [https://covid.cdc.gov/covid-data-tracker/#vaccinations](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

<table>
<thead>
<tr>
<th>Age group</th>
<th>Males (Jul ACIP*)</th>
<th>Males (current**)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TTS cases</td>
<td>Doses admin</td>
</tr>
<tr>
<td>18-29 yrs old</td>
<td>3</td>
<td>1,281,479</td>
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<tr>
<td>30-49 yrs old</td>
<td>4</td>
<td>2,440,773</td>
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<tr>
<td>50-64 yrs old</td>
<td>3</td>
<td>2,130,473</td>
</tr>
<tr>
<td>65+ yrs old</td>
<td>0</td>
<td>943,098</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10</td>
<td>6,795,823</td>
</tr>
</tbody>
</table>


** Current data: vaccination through August 31, 2021

• Source of doses administered: [https://covid.cdc.gov/covid-data-tracker/#vaccinations](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

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

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

*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
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.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)

* CDC Health Alert Network (HAN) notification released on April 13, 2021
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

<table>
<thead>
<tr>
<th>Age group</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TTS deaths</td>
<td>Doses admin</td>
</tr>
<tr>
<td>18-29 yrs old</td>
<td>0</td>
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<tr>
<td>65+ yrs old</td>
<td>0</td>
<td>1,096,923</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7</td>
<td>6,335,437</td>
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</tbody>
</table>

*Source of doses administered: [https://covid.cdc.gov/covid-data-tracker/#vaccinations](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