Johnson & Johnson/Janssen COVID-19 Vaccine and Thrombosis with Thrombocytopenia Syndrome (TTS): Update for Clinicians

Clinician Outreach and Communication Activity (COCA) Webinar

Tuesday, April 27, 2021

Continuing Education

- Continuing education is not offered for this webinar.

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Today's Presenters

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Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine

Clinician Outreach and Communication Activity (COCA) call
April 27, 2021

Tom Shimabukuro, MD, MPH, MBA
CDC COVID-19 Vaccine Task Force
Vaccine Safety Team

Disclaimer

- 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 (CDC) or the U.S. Food and Drug Administration (FDA)
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC or FDA

Topics

- Background
- Thrombosis with thrombocytopenia syndrome following Johnson & Johnson's Janssen COVID-19 vaccine
- Summary

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 therapy or birth control pills, pregnancy, smoking, cancer, older age, etc.
- 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
- Platelets stop bleeding by clumping and forming plugs in blood vessel injuries
- Thrombocytopenia is a condition in which you have a low blood platelet count (<150,000 per microliter)
- Dangerous internal bleeding can occur when your platelet count falls below 10,000 platelets per microliter
- 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

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

News 07/04/2021

EMA confirms overall benefit-risk remains positive

EMA's safety committee (PRAC) has concluded today that unusual blood clots with low blood platelets should be listed as very rare side effects of Vaxzevria (formerly COVID-19 Vaccine AstraZeneca).

In reaching its conclusion, the committee took into consideration all currently available evidence, including the advice from an ad hoc expert group.

EMA is reminding healthcare professionals and people receiving the vaccine to remain aware of the possibility of very rare cases of blood clots combined with low levels of blood platelets occurring within 2 weeks of vaccination. So far, most of the cases reported have occurred in women under 60 years of age within 2 weeks of vaccination. Based on the currently available evidence, specific risk factors have not been confirmed.

People who have received the vaccine should seek medical assistance immediately if they develop symptoms of this combination of blood clots and low blood platelets (see below).

The PRAC noted that the blood clots occurred in veins in the brain (cerebral venous sinus thrombosis, CVST) and the abdomen (splanchnic vein thrombosis) and in arteries, together with low levels of blood platelets and sometimes bleeding.

The Committee carried out an in-depth review of 62 cases of cerebral venous sinus thrombosis and 24 cases of splanchnic vein thrombosis reported in the EU drug safety database (EudraVigilance) as of 22 March 2021, 18 of which were fatal.[1] The cases came mainly from spontaneous reporting systems of the EEA and the UK, where around 25 million people had received the vaccine.

COVID-19 is associated with a risk of hospitalisation and death. The reported combination of blood clots and low blood platelets is very rare, and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of side effects.

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

Originally presented April 14, 2021

National Center for Immunization & Respiratory Diseases

Reports of cerebral venous sinus thrombosis with thrombocytopenia after Janssen COVID-19 vaccine

Advisory Committee on Immunization Practices (ACIP)
April 14, 2021

Tom Shimabukuro, MD, MPH, MBA
CDC COVID-19 Vaccine Task Force
Vaccine Safety Team

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04/03-COVID-Shimabukuro-508.pdf

Cerebral venous sinus anatomy

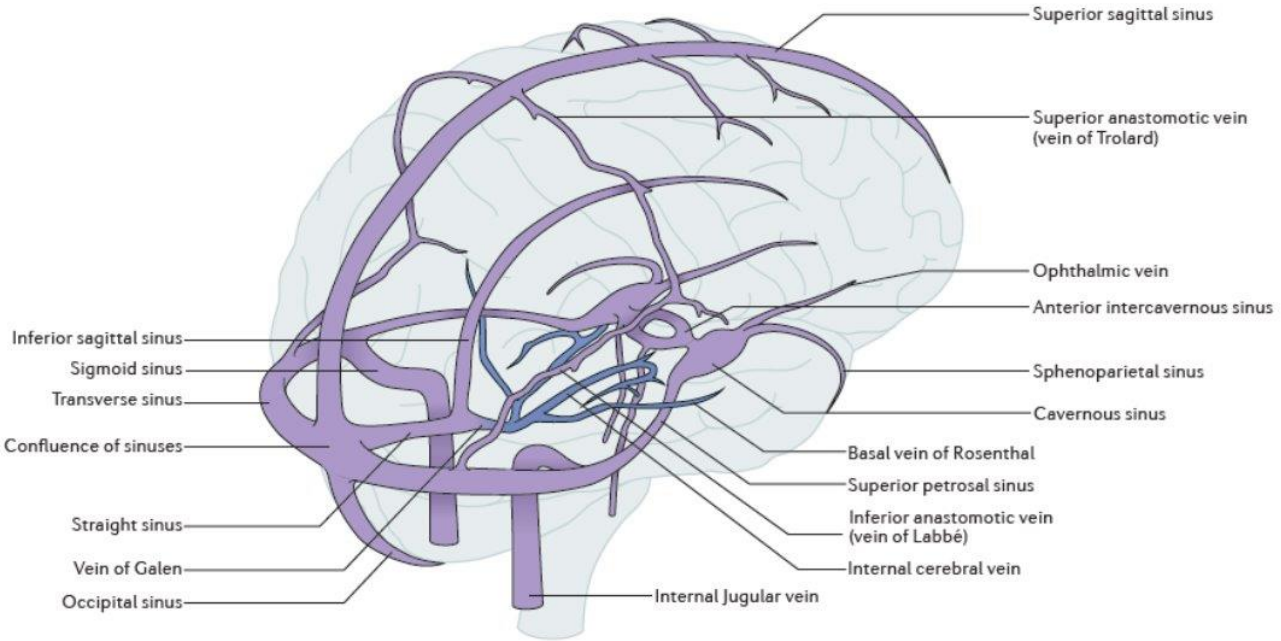


Figure 1 | **Anatomy of the cerebral venous system.** Diagram showing the main components of the cerebral venous system. Blue vessels represent the deep venous system.

Silvis SM et al, Nature Reviews Neurology 13, 555-565(2017)

VAERS data for cerebral venous sinus thrombosis (CVST) reports following COVID-19 vaccines (ACIP April 14, 2021)

Originally presented April 14, 2021

Reports of CVST to VAERS after COVID-19 vaccines as of April 12, 2021

- Janssen COVID-19 vaccine
  - 6 reports of CVST with thrombocytopenia (platelet counts <150K/mm^3) following 6.86 million doses administered
    - Reporting rate of 0.87 cases per million doses administered
- Pfizer-BioNTech COVID-19 vaccine
  - 0 reports following 97.9 million doses administered
- Moderna COVID-19 vaccine
  - 3 reports following 84.7 million doses administered
  - All 3 with normal platelet counts; onset 2, 6, and 12 days after vaccination

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

14

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04/03-COVID-Shimabukuro-508.pdf

CVST with thrombocytopenia following COVID-19 vaccines
(conclusions from ACIP April 14, 2021)

Originally presented April 14, 2021

Summary

- CVST is rare, but clinically serious, and can result in substantial morbidity and mortality; not usually associated with thrombocytopenia
- Observed cases following Janssen COVID-19 vaccines appear to exceed expected based on background rates of CVST among women aged 20–50 years (3-fold or greater)
  - All 6 reports were in women age range 18–48 years, all with thrombocytopenia
  - No obvious patterns of risk factors detected
- CVST with thrombocytopenia has not been observed after the two authorized mRNA vaccines
  - 182 million mRNA COVID-19 doses administered with no reported cases to date
- Clinical features of Janssen cases are similar to those observed following the AstraZeneca COVID-19 vaccine in Europe
- Both Janssen and AstraZeneca vaccines contain replication-incompetent adenoviral vectors (human [Ad26.COV2.S] for Janssen and chimpanzee [ChAdOx1] for AstraZeneca) 24

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-04/03-COVID-Shimabukuro-508.pdf

This is an official

CDC HEALTH ALERT

Distributed via the CDC Health Alert Network
April 13, 2021, 1:00 PM ET
CDCHAN-00442

Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine

Summary
As of April 12, 2021, approximately 6.85 million doses of the Johnson & Johnson (J&J) COVID-19 vaccine (Janssen) have been administered in the United States. The Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) are reviewing data involving six U.S. cases of a rare type of blood clot in individuals after receiving the J&J COVID-19 vaccine that were reported to the Vaccine Adverse Events Reporting System (VAERS). In these cases, a type of blood clot called cerebral venous sinus thrombosis (CVST) was seen in combination with low levels of blood platelets (thrombocytopenia). All six cases occurred among women aged 18–48 years. The interval from vaccine receipt to symptom onset ranged from 6–13 days. One patient died. Providers should maintain a high index of suspension for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the J&J COVID-19 vaccine. When these specific type of blood clots are observed following J&J COVID-19 vaccination, treatment is different from the treatment that might typically be administered for blood clots. Based on studies conducted among the patients diagnosed with immune thrombotic thrombocytopenia after the AstraZeneca COVID-19 vaccine in Europe, the pathogenesis of these rare and unusual adverse events after vaccination may be associated with platelet-activating antibodies against platelet factor-4 (PF4), a type of protein. Usually, the anticoagulant drug called heparin is used to treat blood clots. In this setting, the use of heparin may be harmful, and alternative treatments need to be given.

CDC will convene an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on Wednesday, April 14, 2021, to further review these cases and assess potential implications on vaccine policy. FDA will review that analysis as it also investigates these cases. Until that process is complete, CDC and FDA are recommending a pause in the use of the J&J COVID-19 vaccine out of an abundance of caution. The purpose of this Health Alert is, in part, to ensure that the healthcare provider community is aware of the potential for these adverse events and can provide proper management due to the unique treatment required with this type of blood clot.

Background
VAERS is a national passive surveillance system jointly managed by CDC and FDA that monitors adverse events after vaccinations. The six patients (after 6.85 million vaccine doses administered) described in these VAERS reports came to attention in the latter half of March and early April of 2021 and developed symptoms a median of 9 days (range = 6–13 days) after receiving the J&J COVID-19 vaccine. Initial presenting symptoms were notable for headache in five of six patients, and back pain in the sixth who subsequently developed a headache. One patient also had abdominal pain, nausea, and vomiting. Four developed focal neurological symptoms (focal weakness, aphasia, visual disturbance) prompting presentation for emergency care. The median days from vaccination to hospital admission was 15 days (range = 10–17 days). All were eventually diagnosed with

https://emergency.cdc.gov/han/2021/han00442.asp

Vaccine Safety Datalink (VSD) supplementary analysis for mRNA vaccines

- 2.7 million doses of Pfizer-BioNTech and 2.5 million doses of Moderna COVID-19 vaccine doses administered in VSD as of April 17, 2021
  - 10 total cases of CVST identified following mRNA vaccines
    - 5 cases ruled out (historical n=2, history of head injury n=2, chronic cavernous sinus syndrome n=1)
    - 5 cases potentially CVST, but all <u>without</u> thrombocytopenia
- No confirmed cases of incident CVST with thrombocytopenia after 5.2 million doses of mRNA COVID-19 vaccines administered in VSD

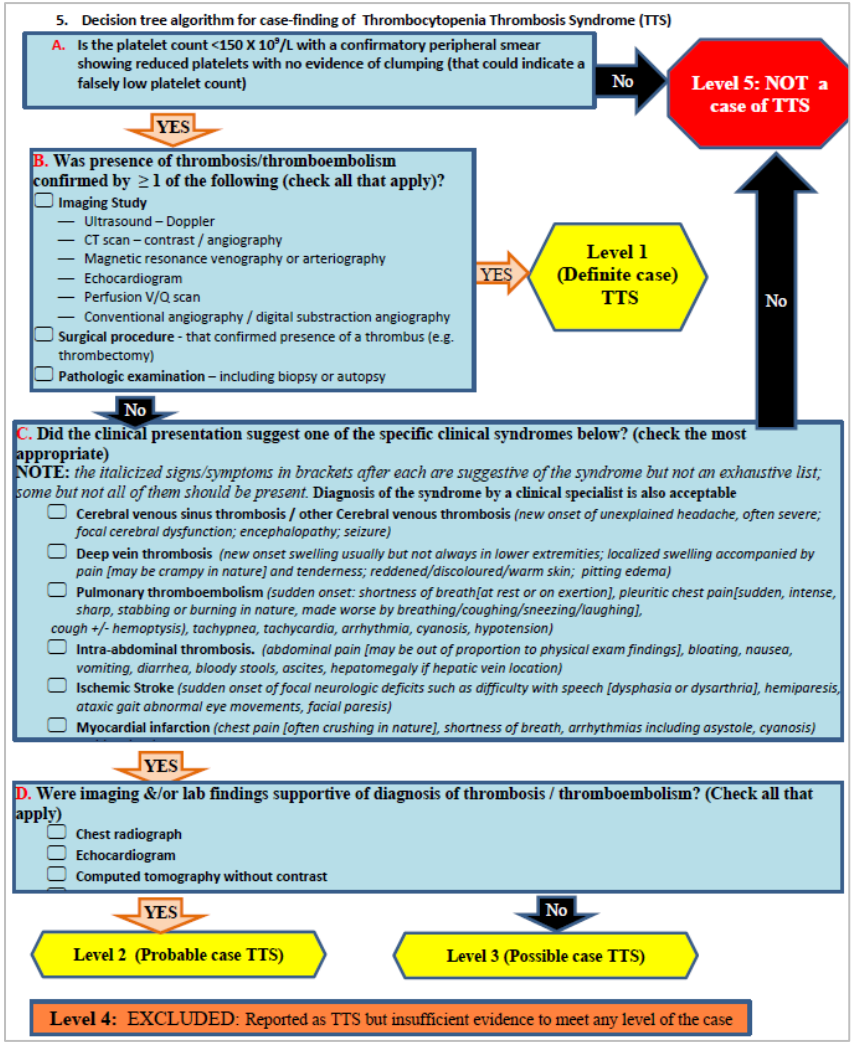
COVID-19 vaccines and CVST with thrombocytopenia

- Safety signal detected for CVST with thrombocytopenia following Janssen COVID-19 vaccine
  - 6 cases observed in women aged 18–48 years in early post-authorization monitoring
  - 1 case observed in pre-authorization clinical trials in a 25-year-old male*
- Currently, there is a lack of evidence of an association between mRNA COVID-19 vaccines and CVST with thrombocytopenia

* https://www.nejm.org/doi/full/10.1056/NEJMc2106075; https://www.fda.gov/media/146217/download

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

Data sources and TTS cases

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

CDC + FDA

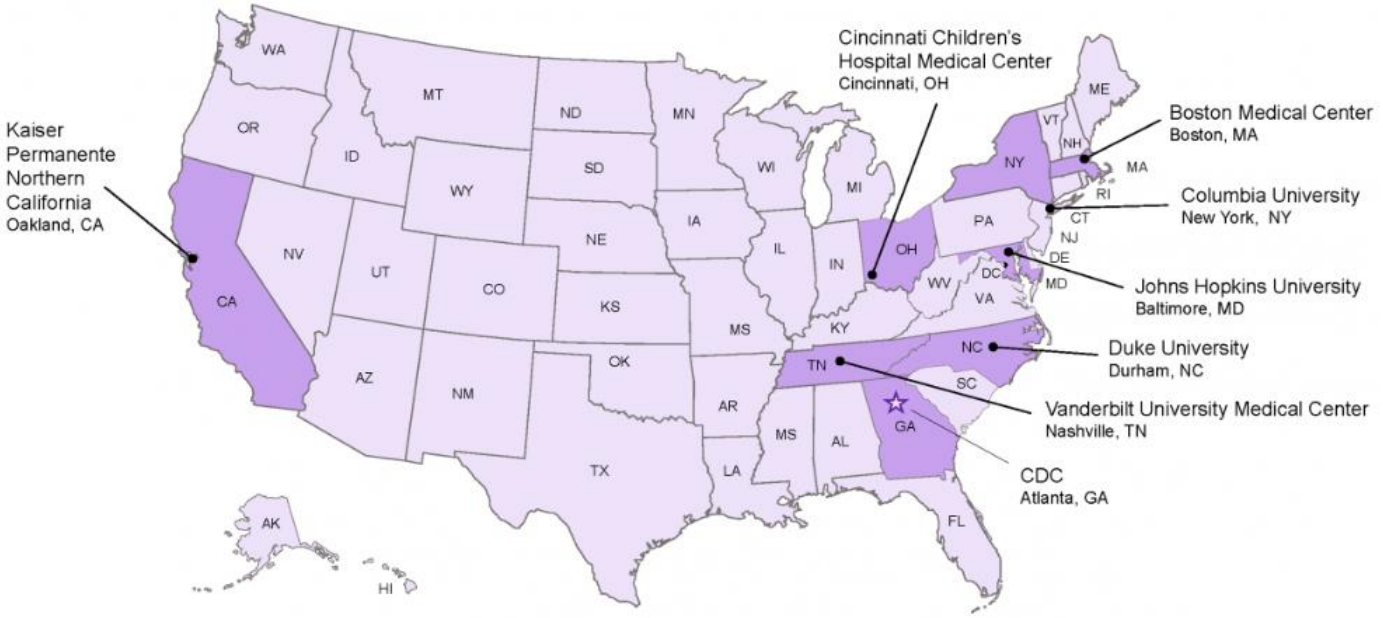
VAERS

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 for TTS following Janssen COVID-19 vaccine

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

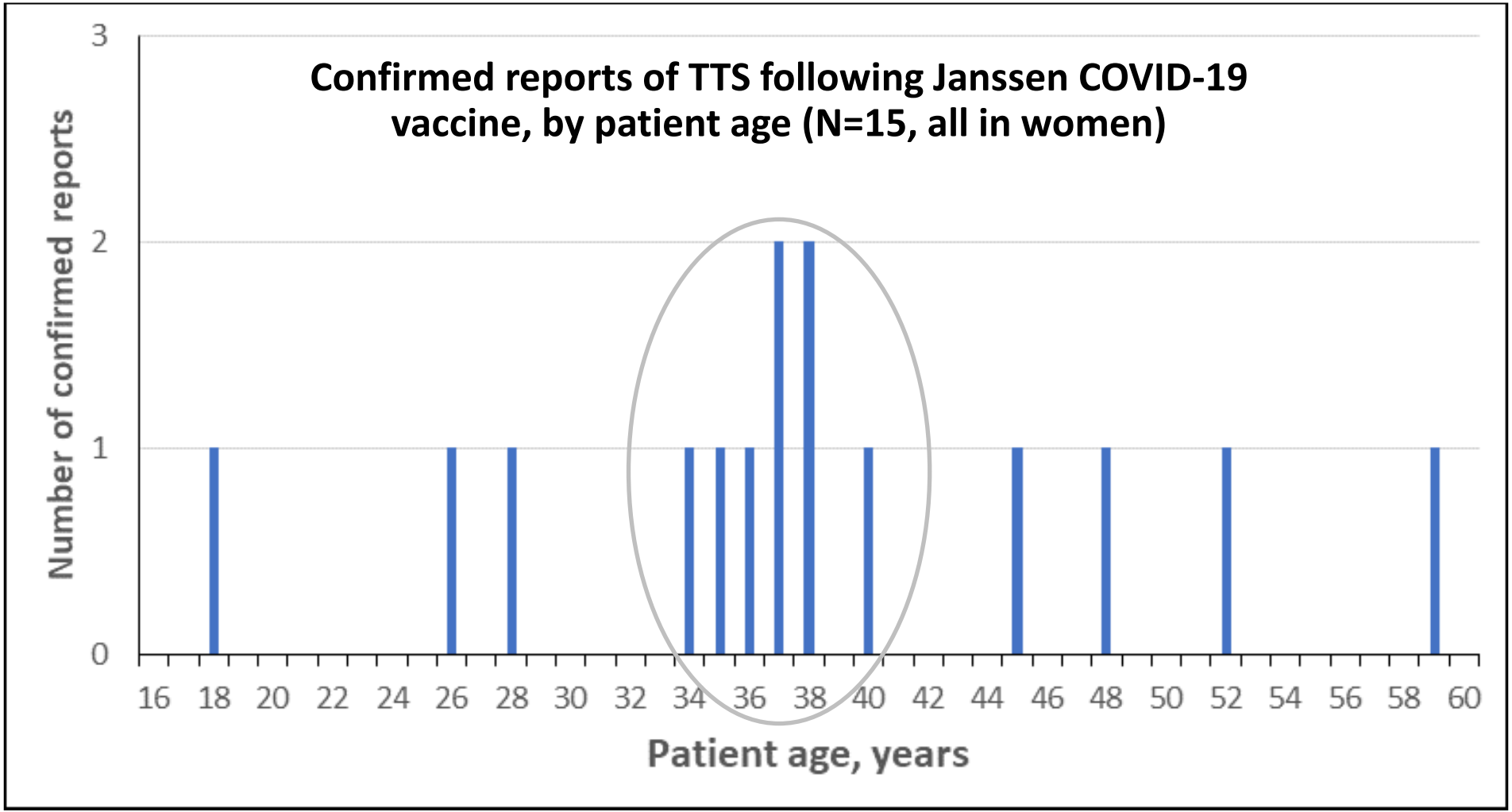
* e.g., acute myocardial infarction, ischemic stroke, deep vein thrombosis, pulmonary embolism

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 was excluded from the final analysis: a female aged <50 years who 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

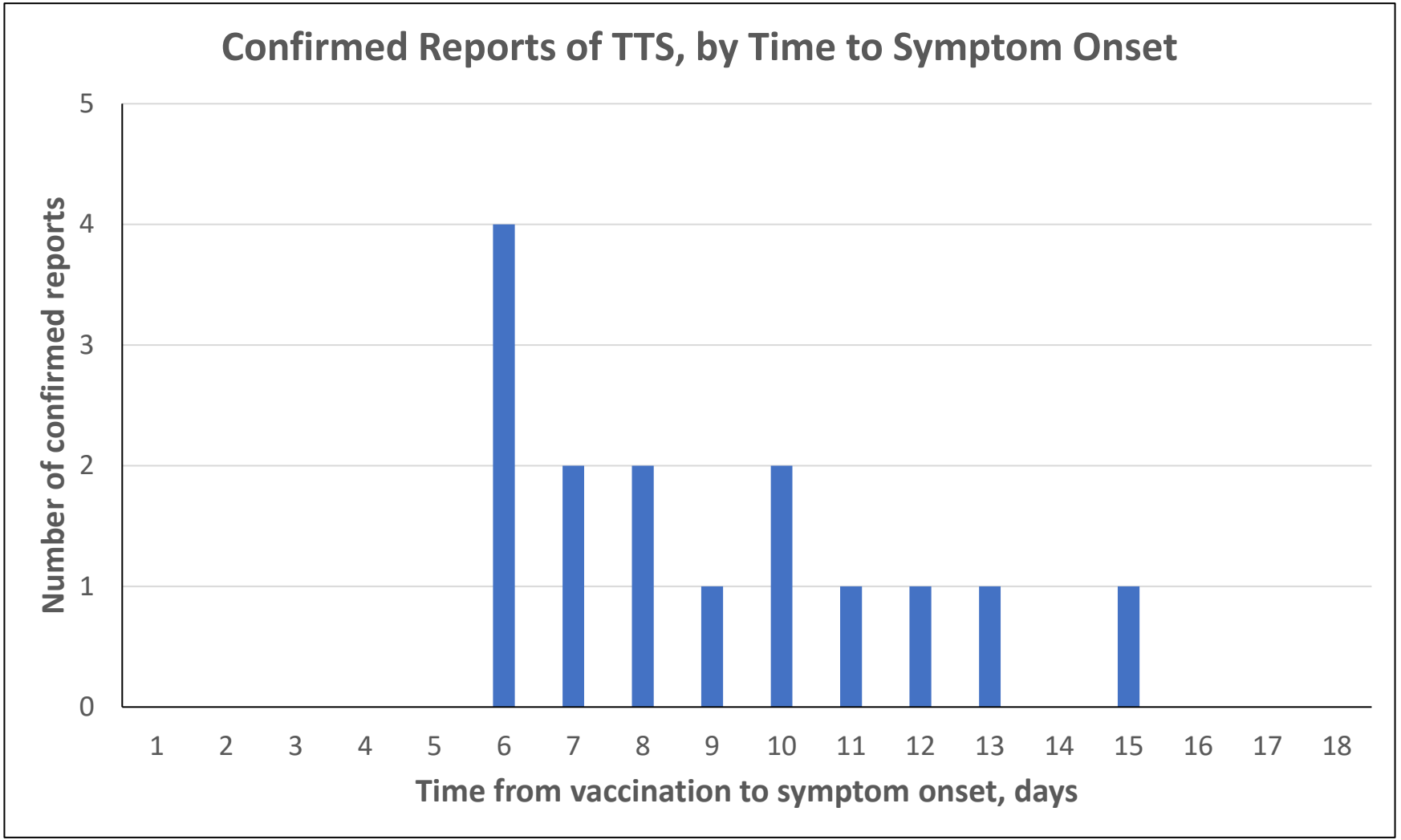
	Females		
Age group	**TTS cases**	**Doses admin**	**Reporting rate‡**
18-29 years old	**3**	579,709	5.2 per million
30-39 years old	**7**	594,215	11.8 per million
40-49 years old	**3**	692,370	4.3 per million
50-64 years old	**2**	1,367,529	1.5 per million
65+ years old	**0**	757,710	0 per million

* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; † One case was excluded from the final analysis: a female aged <50 years who 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
- 12 cases were cerebral venous sinus thrombosis (CVST)
- Pregnant or post-partum* (n=0)
- COVID-19 disease (n=2); both by history, no documentation of serology testing
- 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, by Time to Symptom Onset
Number of confirmed reports
0
1
2
3
4
5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Time from vaccination to symptom onset, days

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***
  - Severe headache, several with neck pain or stiffness
  - Nausea/vomiting
  - Abdominal pain
  - Unilateral weakness
  - Speech difficulty
  - Gaze deviation
  - Loss of consciousness
  - Seizure

* Occurring in ≥2 patients

Locations of thromboses in TTS 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 veins

- **Other locations (n=11)**
  - 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 junction, temporal lobe, frontal lobe, occipital lobe, cerebellum, intraventricular, subarachnoid

† Patients without CVST had thrombosis in these locations

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

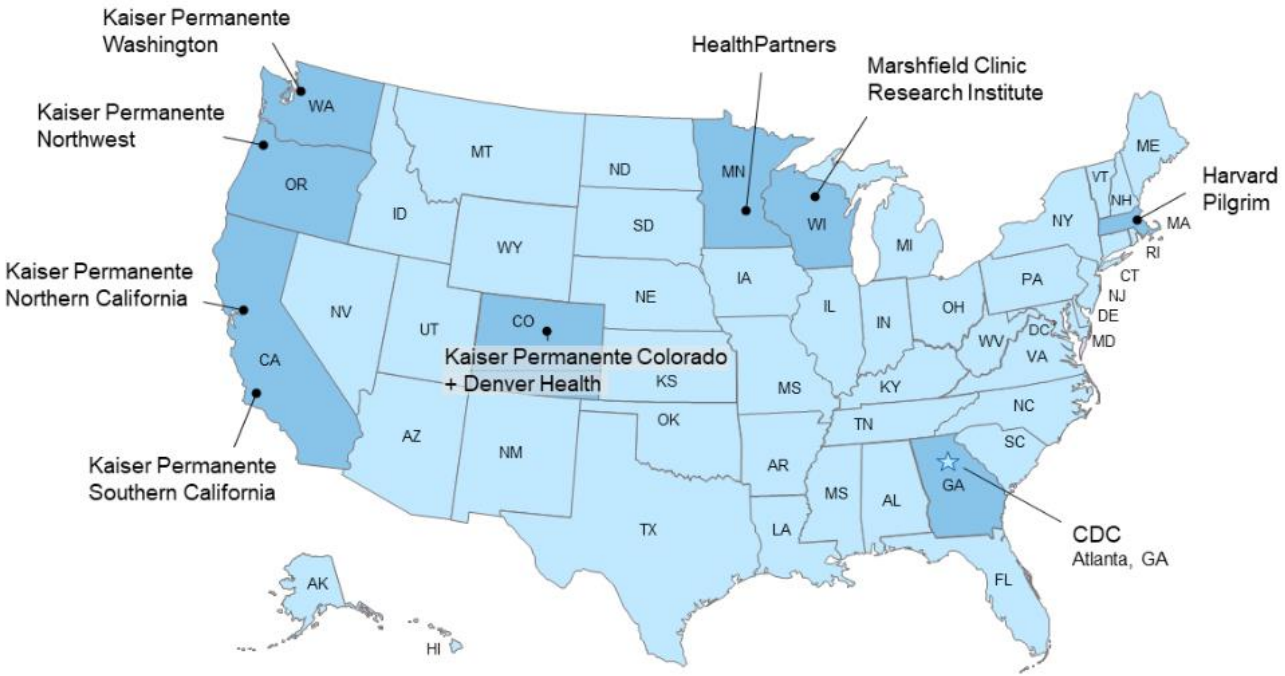
- **Treatment***
  - Heparin (n=6)‡
  - Nonheparin anticoagulants (n=12)
  - Platelet transfusion (n=7)
  - Intravenous immunoglobulin (n=8)

- **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
‡ All patients who received heparin were hospitalized before HAN release
§ None of the patients who died received heparin

VSD

Vaccine Safety Datalink



- **9** participating integrated healthcare organizations
- Data on over **12 million** persons per year

VSD: Thrombosis events after Janssen COVID-19 vaccine

- 142,122 Janssen COVID-19 vaccine doses administered in VSD through April 17, 2021
  - No statistical signals detected for any prespecified Rapid Cycle Analysis outcomes
- No CVST cases identified
- 22 VTE/PE cases identified in the 1–42 days following vaccination and quick reviewed (including 2 with both VTE and PE)
  - 6 ruled out as not VTE
  - 16 were confirmed VTE/PE cases
    - 4 (3 PE, 1 VTE) had symptom onset prior to vaccination
      - Including 1 case with thrombocytopenia documented prior to vaccination
    - 1 had an indeterminate symptom onset
    - 11 were incident cases following vaccination
      - ✓ 6 female (2 PE, 4 VTE), 5 male (1 PE, 4 VTE)
      - ✓ Ages ranged from 50-79 years
      - ✓ None with history of COVID-19 infection
      - ✓ None with thrombocytopenia at time of VTE/PE

VTE = venous thromboembolism

PE = pulmonary embolism

Summary and next steps

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
- It is important to recognize TTS early and initiate appropriate treatment
  - **Do not treat TTS with heparin, unless HIT testing is negative**
- The U.S. vaccine safety monitoring system is able to rapidly detect rare adverse events following immunization and quickly assess safety signals
- Safety surveillance and research on TTS continues
- CDC is committed to open and transparent communication of vaccine safety information

Next Steps

- Continue enhanced monitoring in VAERS and surveillance in other vaccine safety systems (e.g., VSD, CMS, VA electronic health record)
- Expand VAERS database search strategy for TTS reports (proposed)
  - MedDRA PTs for large vessel thrombosis and embolism (all reports regardless of presence of thrombocytopenia)
  - MedDRA PTs for more common thrombotic events AND MedDRA PTs for thrombocytopenia OR text string for “thrombocytopenia” or “low platelets”
  - Medical record review for all potential TTS cases reports to confirm thrombosis with thrombocytopenia

How to report an adverse event to VAERS

- Go to vaers.hhs.gov
- Submit a report online
- For help:

  Call 1-800-822-7967

  Email info@VAERS.org

  video instructions
  https://youtu.be/sbCWhcQADFE

- Please send records to VAERS ASAP if contacted and asked
  - HIPAA permits reporting of protected health information to public health authorities including CDC and FDA

Acknowledgments

We wish to acknowledge the contributions of investigators from the following organizations:

Centers for Disease Control and Prevention

COVID-19 Vaccine Task Force

COVID-19 Vaccine Task Force, Vaccine Safety Team

Immunization Safety Office

Division of Healthcare Quality Promotion

Clinical Immunization Safety Assessment Project

Vaccine Safety Datalink

Food and Drug Administration

Center for Biologics Evaluation and Research

Questions

Back-up Slides

One report of TTS excluded from case count

- Female aged <50 years with COVID-19 (PCR positive) and TTS with complex clinical course:
  - Received Janssen vaccine
  - Hospitalization 1 (admitted 22 days after vaccination): for COVID-19 pneumonia
    - Presented with nausea, hematemesis, shortness of breath; date of symptom onset unclear
    - Normal platelet count
  - Hospitalization 2 (readmitted 28 days after vaccination):
    - Presented with nausea, hematemesis, abdominal pain, shortness of breath, cough
    - Platelet 100,000
    - Imaging studies showed CVST, lower leg venous thromboembolism, pulmonary embolism
    - Died during hospitalization*

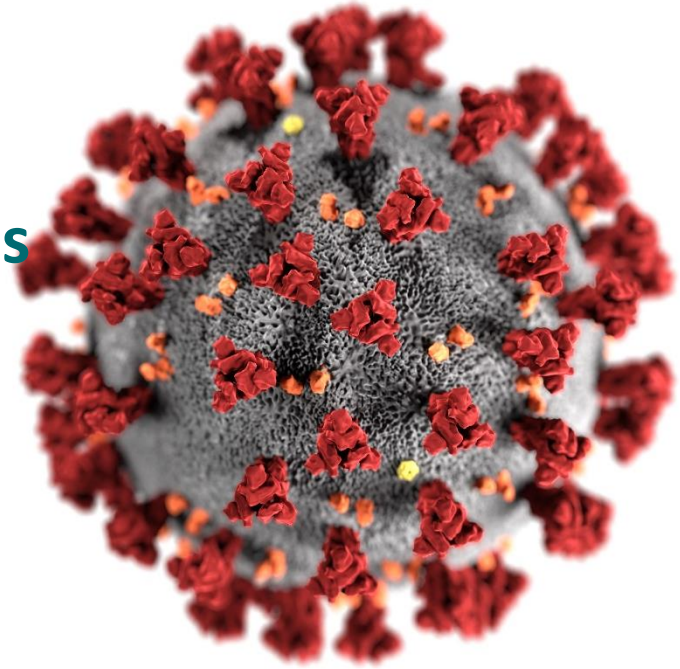
*Reported cause of death: respiratory failure, shock, COVID-19 pneumonia

Proposed VAERS MedDRA PT and text string search terms for TTS

- **MedDRA PTs for large vessel thrombosis and embolism**
  - Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis
- **MedDRA PTs for more common thrombotic events**
  - Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, MedDRA PTs for acute myocardial infarction*, MedDRA PTs for stroke*
- **MedDRA PTs for thrombocytopenia**
  - Autoimmune heparin-induced thrombocytopenia, Heparin-induced thrombocytopenia, Immune thrombocytopenia, Non-immune heparin associated thrombocytopenia, Spontaneous heparin-induced thrombocytopenia syndrome, Thrombocytopenia, Thrombocytopenic purpura
- **Text string for**
  - “thrombocytopenia” or “low platelets” in symptom text

* https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf

Risk/Benefit assessment of thrombotic thrombocytopenic events after Janssen COVID-19 vaccination



Sara Oliver MD, MSPH

COCA Call

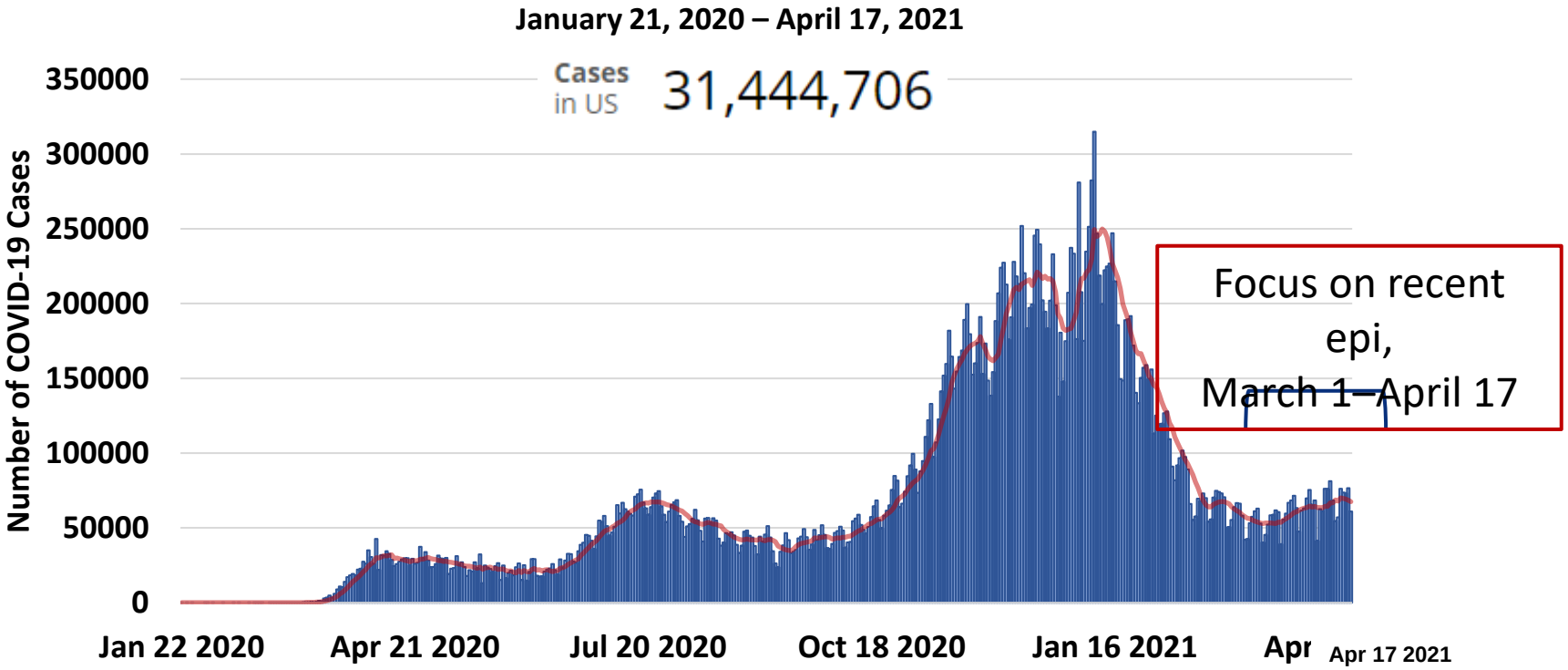
April 27, 2021

Data reviewed to inform the Risk/Benefit Analysis

- Recent COVID-19 Epidemiology
- Epidemiology of other relevant clinical conditions
  - Cerebral Venous Sinus Thrombosis (CVST); Heparin Induced Thrombocytopenia (HIT); Thrombosis after COVID-19 Disease
- Benefits and potential harms of Janssen COVID-19 vaccine
- Benefit/Risk Assessment of COVID-19 vaccines
  - Population-Level Risk/Benefit Assessment
  - Individual-Level Risk/Benefit Assessment
- Values and Acceptability
- Feasibility and Equity

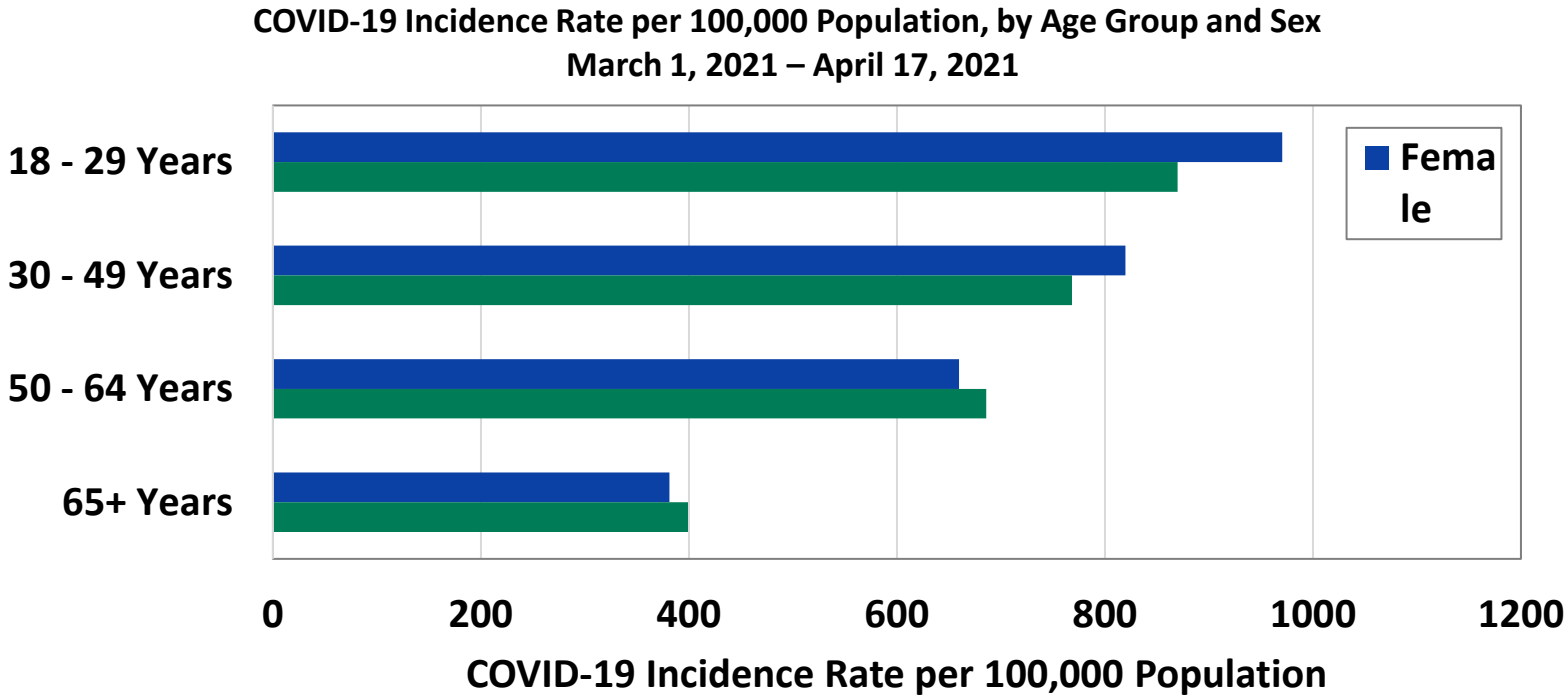
Recent COVID-19 Epidemiology

Trends in Number of COVID-19 Cases in the US



https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

COVID-19 Incidence Rates, by Age Group and Sex



https://covid.cdc.gov/covid-data-tracker/#demographics

Summary of the COVID-19 Epidemiology

March 1–April 17, 2021

- **Incidence**
  - Cumulative incidence rate for adults: **710.9** per 100,000 population
  - Younger females (18-29 years) have the highest incidence of new infections
- **Hospitalization**
  - Cumulative hospitalization rate for adults: **20.6** per 100,000 population
  - Most hospitalizations still occur in persons aged ≥ 65 years
    - Proportion of hospitalizations occurring in persons aged ≥65 years declining
- **Mortality**
  - Cumulative mortality rate: **3.0** per 100,000 population
  - Most COVID-19 deaths still occur in persons aged ≥ 65 years
    - Proportion of deaths occurring in persons aged ≥65 years declining

https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html . https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html . https://covid.cdc.gov/covid-data-tracker/#trends_totalandratedeathssevendayrate

Epidemiology of other relevant clinical conditions

Epidemiology of Cerebral Venous Sinus Thrombosis (CVST)

- Cerebral Venous Sinus Thrombosis (CVST) incidence: **14.5–28.5** per million U.S population
  - Incidence increasing in recent years (4% annually)
  - Higher in women aged 18–49 years
  - Risk factors (e.g., hereditary thrombophilia, oral contraceptives, obesity) identified in up to 85% of cases
  - Mortality ~5-10%

- Incidence with thrombocytopenia much lower than without thrombocytopenia
  - CVST with thrombocytopenia: **0.7–1.6** per million U.S. population

Data source: Health Care Utilization Project (HCUP) National Inpatient Sample (NIS) for 2018 and Marketscan Treatment Pathways (Continuously-enrolled Commercial Insurance and Medicaid) for 2019

Otite et al. Neurology 2020; 95: e2200-e2213. 2020; Silvis et al. *Nat Rev Neurol* 13, 555–565 (2017). Silvis et al. *Semin Thromb Hemost* 2016;42:622–631.;

Heparin-Induced Thrombocytopenia with Thrombosis (HITT)

- Heparin-induced thrombocytopenia (HIT) occurs in 0.5% to 1% of patients exposed to unfractionated heparin for medical and surgical indications
  - Incidence: **23–45** per million total U.S. population*
- Of patients with HIT, thrombosis occurs in about 20%−64% (called HITT)
- Immune mediated — antibodies against platelet factor 4 (PF4) & heparin
- Risk factors for developing thrombosis
  - Genetic polymorphisms
  - Lower platelet count (and earlier fall in count)
  - Higher titer of anti-heparin/PF4 antibodies
  - Prior surgery (cardiac, orthopedic, trauma)
  - Cardiovascular disease

* Source: HCUP NIS 2018 and Marketscan (Continuously-enrolled Commercial Insurance and Medicaid) for 2019, unable to distinguish autoimmune HIT vs heparin-induced HIT

Arepally et al. 2021. https://www.ahajournals.org/doi/epub/10.1161/ATVBAHA.120.315445; Nand et al. 1998 https://doi.org/10.1002/(SICI)1096-8652(199709)56:1<12::AID-AJH3>3.0.CO;2-5; Fabris et al 2002. https://onlinelibrary.wiley.com/doi/epdf/10.1046/j.1365-2796.2002.01021.x ; Greinacher et al. 2005. https://www.thieme-connect.com/products/ejournals/abstract/10.1160/TH04-12-0825

CVST associated with COVID-19

- Systematic review and meta-analysis of CVST among patients hospitalized for COVID-19
  - Estimates between **0.03%** and **0.08%** of hospitalized COVID-19 patients
- Estimated risk of **5–6** cases of CVST per million SARS-COV-2 infections*
- CVST + thrombocytopenia in COVID-19 patients is extremely rare
- Pathology appears different than TTS after COVID-19 vaccines
  - PF4/heparin specific antibodies negative by ELISA or platelet functional assay for confirmed COVID-19 patients (n=222), including 10 with thromboembolic complications

* Data source: Premier Healthcare Database, January 2020-January 2021

Acronyms: Cerebral Venous Sinus Thrombosis (CVST), Thrombosis with Thrombocytopenia Syndrome (TTS)

Katsanos et al. (2020) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7753413/ ; Baldini et al. (2021) https://doi.org/10.1111/ene.14727; Mowla et al. (2020) https://doi.org/10.1016/j.jns.2020.117183; Greinacher et al. Research Square preprint (Apr 9, 2021): https://www.researchsquare.com/article/rs-404769/v1

Thrombosis with Thrombocytopenia Syndrome (TTS) after AstraZeneca vaccine in Europe

- European Union: **~10 cases per million** (1 case per 100,000)
  - As of April 4, 2021, **169** cases of CVST & **53** cases of splanchnic vein thrombosis reported to EudraVigilance. ~34 million people vaccinated in EEA & UK by this date.
  - Most of cases in women aged <60 years within 2 weeks of receiving 1st vaccine dose
- European Medicines Agency concluded benefit/risk ratio still favorable to use vaccine

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- United Kingdom: **7.9 per million** (21.2 million AZ doses given)
  - As of April 14: **168 reports** of blood clotting with low platelets
  - **77** CVST with thrombocytopenia; 91 in other major veins with thrombocytopenia
  - 93 women, 75 men, aged 18–93 years
- UK regulatory agencies conclude that benefits continue to outweigh risks
  - Recommended **ages 18–29** years at low risk of infections be offered other vaccines

https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield)

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

https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots

https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement/jcvi-statement-on-use-of-the-astrazeneca-covid-19-vaccine-7-april-2021

Summary

COVID-19

Hospitalization:
200 per million population

Death:
30 per million population

HIT

23–45 per million population

CVST

14.5–28.5 per million population

CVST + Thrombocytopenia

0.7–1.6 per million population

CVST after COVID-19

5-6 per million SARS-COV-2 infections

TTS after AZ vaccine

EU:
10 per million vaccinated population

UK:
7.9 per million vaccinated population

Acronyms: Cerebral Venous Sinus Thrombosis (CVST), Heparin-Induced Thrombocytopenia (HIT), Thrombosis with Thrombocytopenia Syndrome (TTS), AstraZeneca (AZ)

Benefits and Harms

Benefits of the Janssen COVID-19 vaccine

- Efficacy against symptomatic, lab-confirmed COVID-19. Phase III trial: **66%** (95% CI: 60%, 72%)
- **Higher** efficacy against **severe** outcomes than for any symptomatic COVID-19
  - VE against **deaths** due to COVID-19**: 100%**
- Vaccine shipment and storage (3 months) at **refrigerator** temperatures (2-8^{o}C)*
- **Single-dose** series

Potential Harms of the Janssen COVID-19 vaccine

- **7.98 million** vaccine doses administered* and **15** confirmed Thrombosis with Thrombocytopenia Syndrome (**TTS**) cases as of April 21, 2021

	Females			Males		
Age group	**Cases**	**Doses admin**	**Reporting rate†**	**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

* One TTS case occurred in the Phase 3 trial in a male aged 18-49 years.

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS); Vaccine Efficacy (VE)

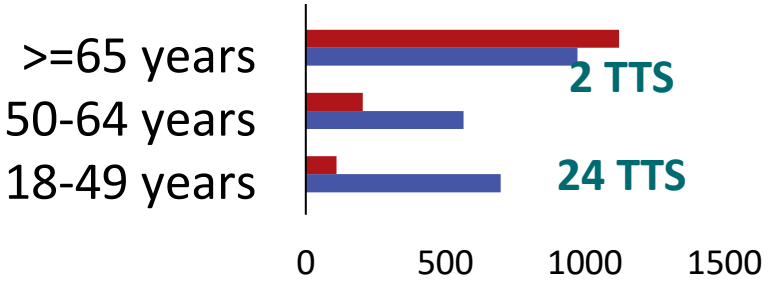
Population Level Risk-Benefit Analysis

Benefits and harms of resuming vaccination for ages ≥18 years vs. ≥50 years over 6-month period

Moderate transmission; Vaccination resumed at 50% of rate before pause

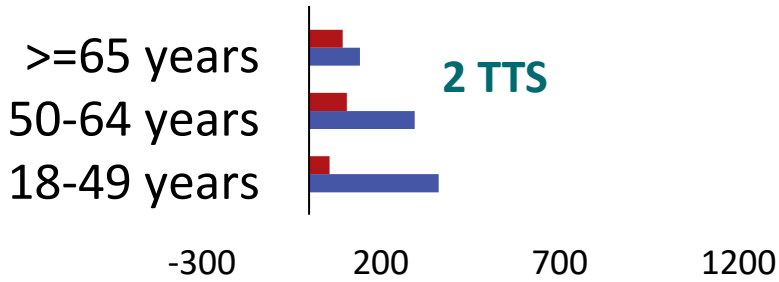
Deaths averted ICU admissions averted

Resume vaccination: age 18+



26 TTS in 9.8M vaccinations
Prevent 1,435 deaths, 2,236 ICU admissions

Resume vaccination: age 50+



2 TTS in 3.6M vaccinations
Prevent 257 deaths, 779 ICU admissions

[1] Based on observed cases adjudicated as of 4/21/2021
NOTE: in Phase III RCT, one male in 18-49 year age group experienced TTS; not included in this analysis
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Summary of population-level risks and benefits by recommendation, all scenarios

Recommendation for all persons aged 18+

- **Risks:** Expect **26–45 TTS** cases, depending on uptake
- **Benefits:** Depend on uptake, amount of transmission
  - **800–3,500 fewer ICU** admissions
  - **600–1,400 fewer deaths**

Recommendation for all persons aged 50+

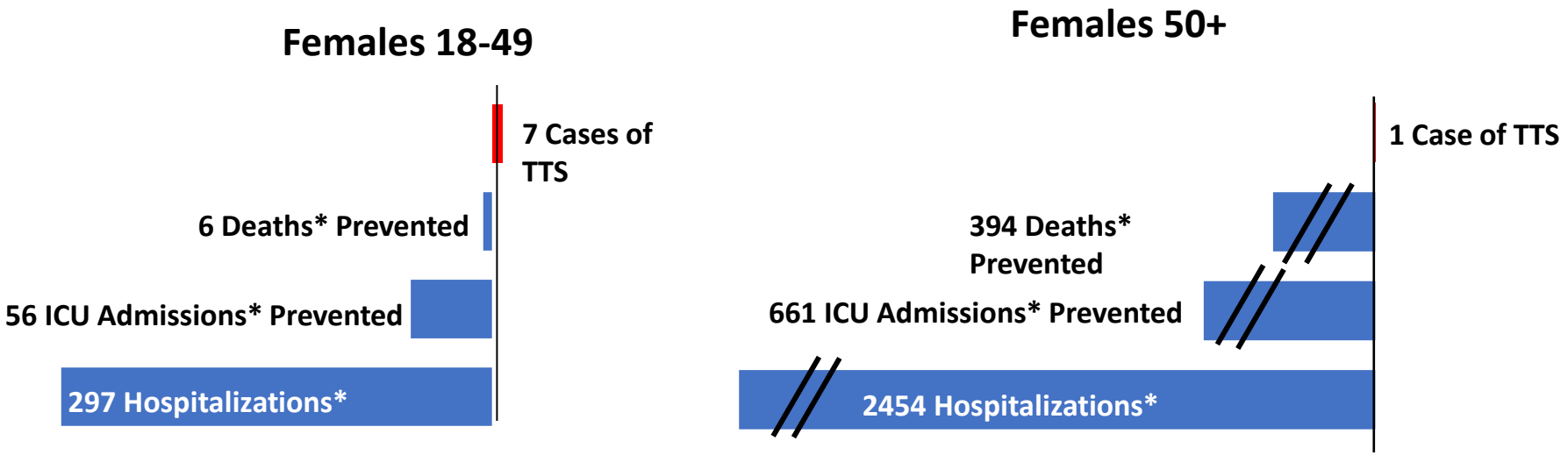
- **Risks:** Expect 2–3 TTS cases, depending on uptake
- **Benefits:** Depend on uptake, amount of transmission
  - **300–1000 fewer ICU** admissions
  - **40–250 fewer deaths**

Note: Benefits of vaccination apply to the whole population over a 6-month period, and result from direct and indirect effects

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Risks and benefits females, by age group

For every **1 million** doses of vaccine given with current US exposure risk[1]



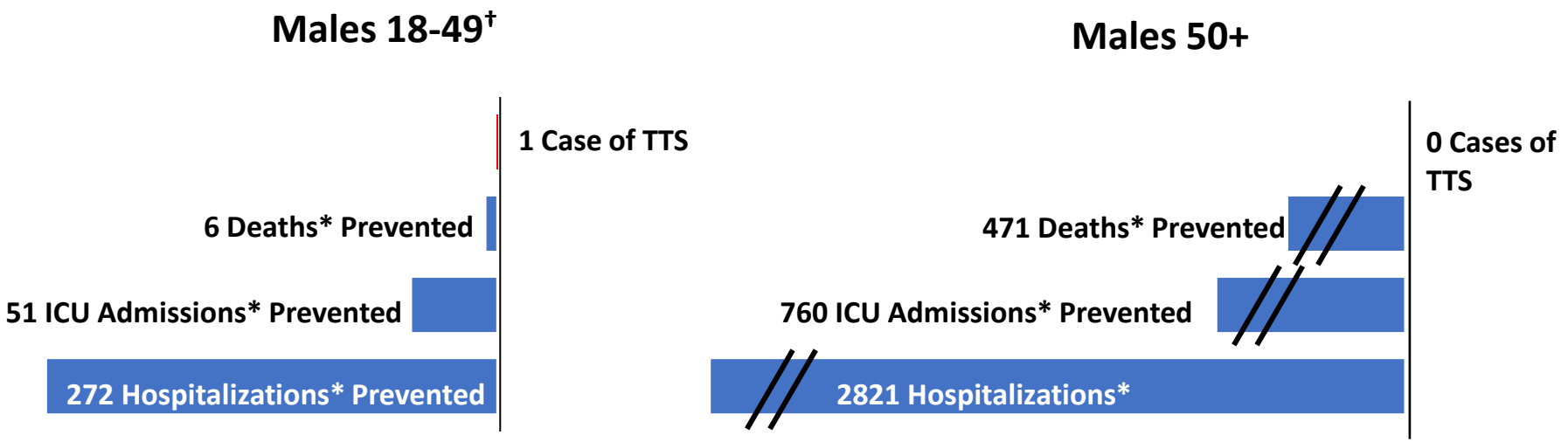
* Deaths, ICU admissions, and deaths due to COVID-19

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Diagonal lines indicate a scale break in y-axis

Risks and benefits males, by age group

For every **1 million** doses of vaccine given with current US exposure risk[1]



†Analyses incorporated one TTS case that occurred in the Phase 3 trial in a male aged 18-49 years.
*Deaths, ICU admissions, and deaths due to COVID-19
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Diagonal lines indicate a scale break in y-axis

Risk-benefit interpretations

- Population
  - Takes into account direct and indirect (herd) effects of vaccination
  - Incorporates availability of different vaccines
  - Simulates incidence, hospitalizations, and deaths over course of pandemic
  - 6-month time horizon
- Shows **large population benefit** of vaccination relative to rare TTS

- Individual
  - Considers individual benefits of vaccination vs. individual risks
  - Only considers getting Janssen vaccine vs. not getting a vaccine
  - Short, 1-month time horizon
- Shows **positive** balance for benefits vs. risks for all age and sex groups
- Balance of risks and benefits **varies** by **age and sex**

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Values and Acceptability

Values and Acceptability:

Intent to receive Janssen COVID-19 vaccine over time

- Only 37% of respondents called the Janssen COVID-19 vaccine safe after the pause was announced[1]
  - Drop of 15% in two to three days

- Americans now much less likely to prefer the Janssen COVID-19 vaccine[2]
  - 13% decline in preference for the Janssen COVID-19 vaccine
  - Declined 9% to 25% across age and race categories

1. https://today.yougov.com/topics/politics/articles-reports/2021/04/15/johnson-johnson-vaccine-confidence
2. CVS Health Survey- COVID-19 Vaccine Brand Preferences and Hesitancy Post J&J Pause

Values and Acceptability:

Effect on overall vaccine confidence

- Drop in vaccine confidence does not appear to extend to the Pfizer-BioNTech and Moderna COVID-19 vaccines[1]
  - 59% consider them safe
  - 19% feel they are unsafe

- Recent poll did not suggest reduction in intent to be vaccinated[2]
  - 40% more likely to receive COVID-19 vaccine compared to one month ago
  - 36% report no change in intent

- A different survey found half of the unvaccinated are less inclined to receive COVID-19 vaccine after the pause, regardless of brand[3]

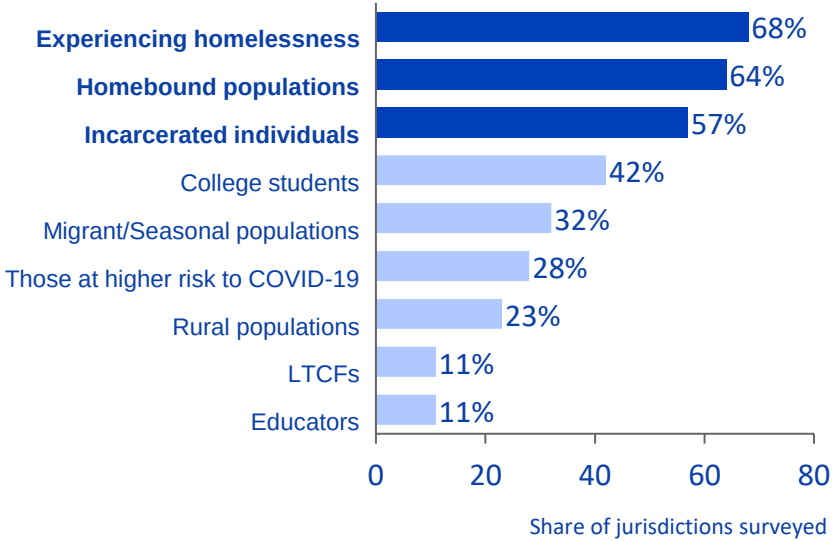
1. https://today.yougov.com/topics/politics/articles-reports/2021/04/15/johnson-johnson-vaccine-confidence
2. deBeaumont Foundation Poll, April 15-16, 2021. Vaccine Confidence Grows Despite J&J Pause
3. CVS Health Survey- COVID-19 Vaccine Brand Preferences and Hesitancy Post J&J Pause

Feasibility and Equity

Feasibility: Jurisdictions' pre-pause use of Janssen COVID-19 vaccine

Populations: Focus on reaching those experiencing homelessness, homebound or currently incarcerated

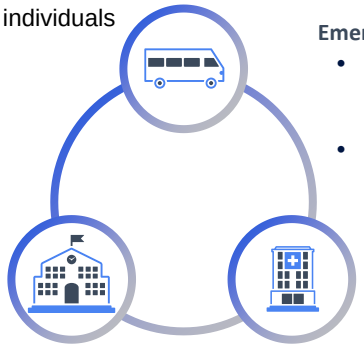
Q: Prior to the pause in administration of the Janssen vaccine, which populations had you focused on vaccinating with this product?



Vaccination settings: Three core settings used by jurisdictions to administer Janssen vaccine

Mobile vaccination

- Temporary PODs and mobile vans able to reach transient, rural and homebound individuals



Emergency departments

- Provided at discharge from urgent care or ER departments
- Particularly for 'safety-net' hospitals reaching transient groups

Student health centers

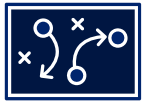
- On-campus vaccination centers with ambition to vaccinate students unable or less likely to return for second dose at end of semester

Jurisdictional survey on impacts of Janssen pause, April 18th- 21st, 2021 (n=53)

Acronyms: Points of Dispensing (PODs)

Feasibility: Impact if Janssen COVID-19 vaccine was no longer recommended

Jurisdictions are particularly concerned about 2nd dose management and equity



Janssen provided flexibility to jurisdictions to…

Avoid additional second dose management, particularly for transient and hard-to-reach populations

Run mobile vaccination clinics without need for return visits

Reduce administrative burden on providers

Fully vaccinate college students before end of school year

Many individuals expressed a preference for Janssen

Convenience of single dose appeals to many recipients

Some individuals hesitant about receiving an mRNA vaccine

Possibility of second dose side effects causes some to favor Janssen

Some providers with lower volumes of patients have preference for single dose vaccine

Greater difficulty serving disproportionately affected populations

Increased challenge to reach homebound, transient, and rural populations because of need to administer second dose

Less flexibility to use mobile vaccination units

Reduced ability to vaccinate upon ED/hospital discharge

Decreased vaccine supply from loss of Janssen could harm vaccine access

Jurisdictional survey on impacts of Janssen pause, April 18th- 21st, 2021 (n=53)

Policy Options

Policy Options for Janssen COVID-19 Vaccine Recommendations

Do **not** recommend use of Janssen vaccine

Recommend use of Janssen vaccine in **all adults** ≥18 years of age

Recommend use of Janssen/J&J COVID-19 vaccine in **some** populations

Policy Options for Janssen Vaccine Policy Recommendations

Work Group Summary

- Detailed discussion of risk/benefit balance difficult in many current vaccination settings
- Recommendations that require vaccination sites to require two types of vaccines would be difficult to implement
- Access to vaccines for hard-to-reach populations remains important
- Risk/benefit balance may change as the pandemic evolves and risk of COVID-19 disease changes

Policy Options for Janssen Policy Recommendations

- Recommend **against** use for all persons
- Reaffirm recommendations for **all** age and sex
  - FDA to include warning statement with EUA
- Recommend vaccination only for adults **≥50 years of age**
- Reaffirm recommendations for use; women aged <50 years should **be aware** of the increased risk of TTS, and **may choose** another COVID-19 vaccine (i.e. mRNA vaccines)

ACIP Vote – Interim Recommendation

The Janssen COVID-19 vaccine is recommended for persons 18 years of age and older in the U.S. population under the FDA's Emergency Use Authorization.

FDA-agreed Warning and Precaution Regarding Thrombosis with Thrombocytopenia

5.2 Thrombosis with Thrombocytopenia

Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination *[see Overall Safety Summary (6.2)]*. Most cases of thrombosis with thrombocytopenia reported following the Janssen COVID-19 Vaccine have occurred in females ages 18 through 49 years; some have been fatal. Specific risk factors for thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine and the level of potential excess risk due to vaccination are under investigation. Based on currently available evidence, a causal relationship between thrombosis with thrombocytopenia and the Janssen COVID-19 Vaccine is plausible.

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

Clinical Considerations

Considerations for use of the Janssen COVID-19 vaccine

- FDA has added a **warning** to the Janssen COVID-19 vaccine EUA and fact sheets regarding rare clotting events that have been reported among vaccine recipients.
- The **EUA fact sheet** should be provided to all vaccine recipients and their caregivers before vaccination with any authorized COVID-19 vaccine.

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

Considerations for use of the Janssen COVID-19 vaccine

Women aged <50 years

- Women aged <50 years can receive any FDA-authorized COVID-19 vaccine
- However, they should be aware of the rare risk of TTS after receipt of the Janssen COVID-19 vaccine, and the availability of other FDA-authorized COVID-19 vaccines (i.e. mRNA vaccines).
- The highest rates of TTS per vaccine doses administered were identified in women <50 years of age

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

Considerations for use of the Janssen COVID-19 vaccine

People with a history of thrombosis or risk factors for thrombosis

- Etiology of TTS appears similar to heparin-induced thrombocytopenia (HIT)
- Until more information becomes available, experts advise that a person with a history of an episode of an immune-mediated syndrome characterized by thrombosis and thrombocytopenia (such as HIT) should be offered **another FDA-authorized COVID-19 vaccine**, for at least **90-180 days** after resolution of their illness

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

Considerations for use of the Janssen COVID-19 vaccine

People with a history of thrombosis or risk factors for thrombosis

- The biologic mechanisms for venous thromboembolism (VTE) and arterial thrombi differ from the underlying immune-mediated mechanism for HIT
- Based on current knowledge, experts believe that people with risk factors for VTE, or a prior history of thromboses **not** associated with thrombocytopenia are **unlikely** to be at increased risk for TTS
- Although the risk of thrombosis is increased during pregnancy and the postpartum period, and with some hormonal contraceptives, experts believe that these factors **do not** make people more susceptible to TTS after receipt of the Janssen COVID-19 vaccine
  - Individuals can receive any FDA-authorized vaccine, including Janssen COVID-19 vaccine

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

Considerations for use of the Janssen COVID-19 vaccine

Use of anticoagulants

- People who take aspirin or anticoagulants as a part of their routine medications do **not** need to **stop** taking these medications prior to receipt of the Janssen COVID-19 vaccine
- It is **not recommended** that people take aspirin or anticoagulants before vaccination with the Janssen COVID-19 vaccine or any other FDA-authorized COVID-19 vaccine

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

Janssen/J&J COVID-19 vaccine:
HAN released April 13, 2021

Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine

- Recommendations for Clinicians: diagnosis and treatment
  - Evaluate patients with a screening **PF4 enzyme-linked immunosorbent (ELISA) assay** as would be performed for autoimmune HIT. Consultation with a hematologist is strongly recommended.
  - **Do not treat with heparin**, unless HIT testing is negative
- Recommendations for Public Health: case reporting through VAERS
  - Encourage healthcare providers and the public to report all serious and life-threatening adverse events and deaths following receipt of COVID-19 vaccines to VAERS
- Recommendations for the Public: clinical signs and symptoms to monitor
  - Contact healthcare provider, or seek medical care if you develop severe headache, abdominal pain, leg pain, or shortness of breath within three weeks after vaccination with the J&J COVID-19 vaccine

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- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

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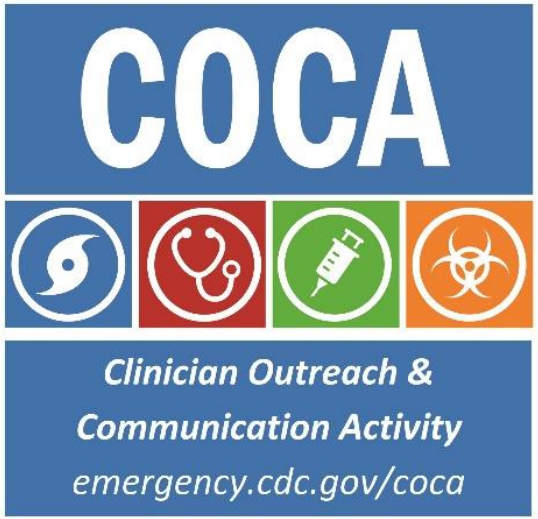

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