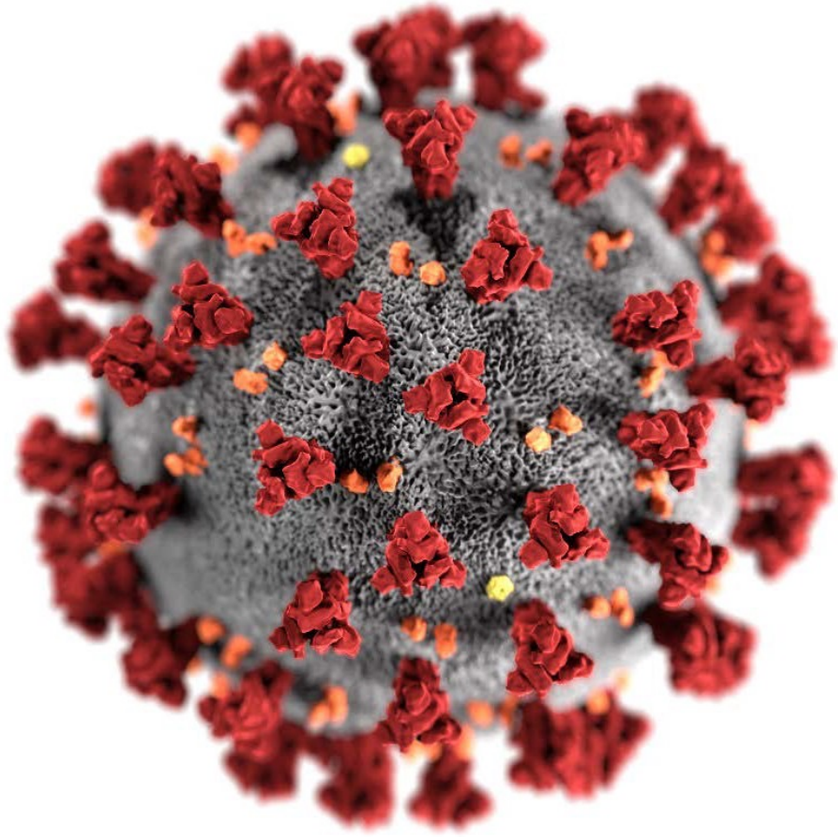
Discussion of thrombocytopenic thrombosis after Janssen vaccine:

- Review of COVID-19 Vaccines
- Summary of ACIP Emergency Meeting, 4-14-21



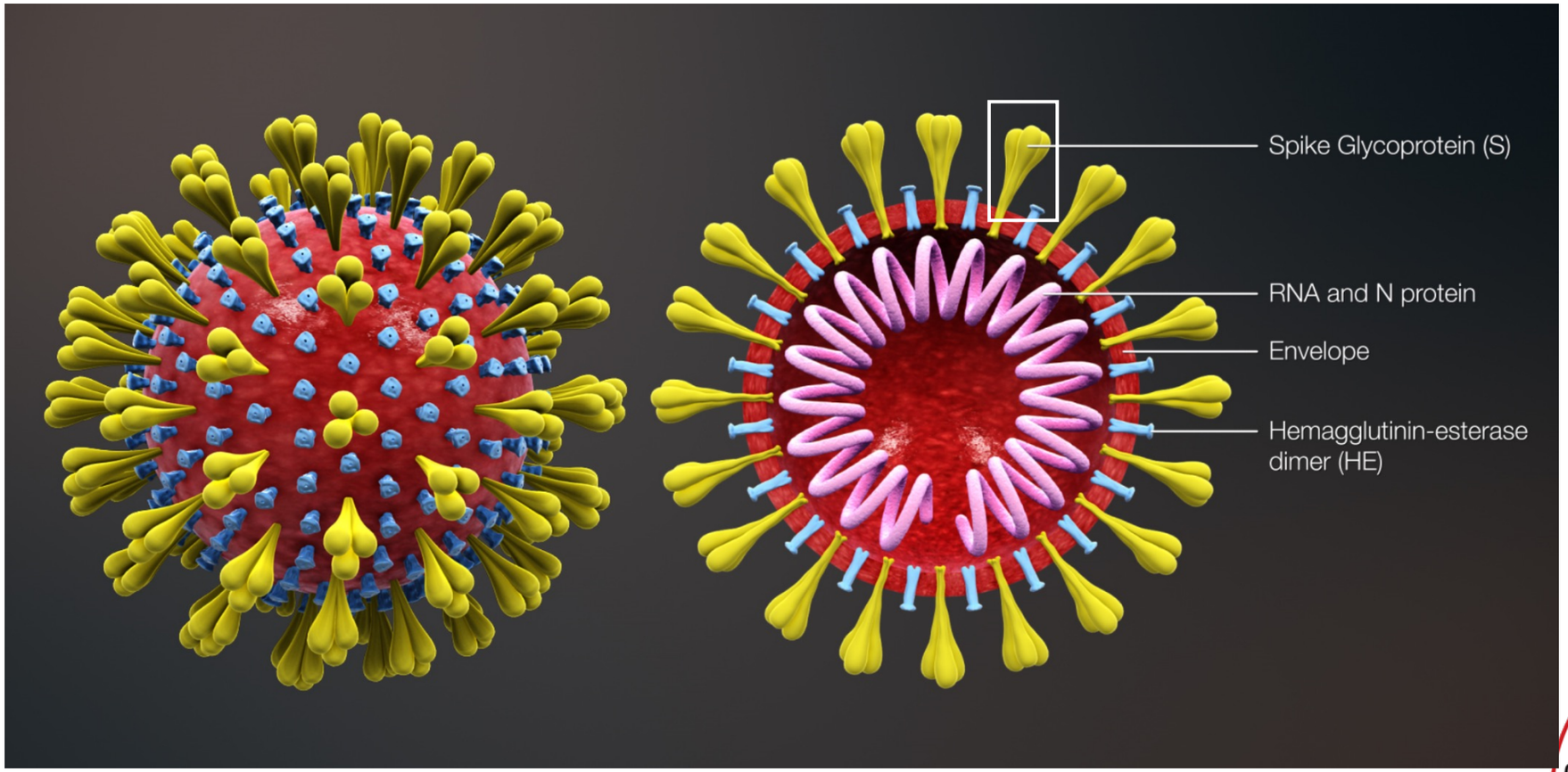
Harry Brown, MD, USET
CAPT Thomas Weiser MD, MPH IHS ACIP
Ex-Officio Representative April 19, 2021

How Do COVID-19 Vaccines Work?

There are 2 types of vaccines currently in use in the US:

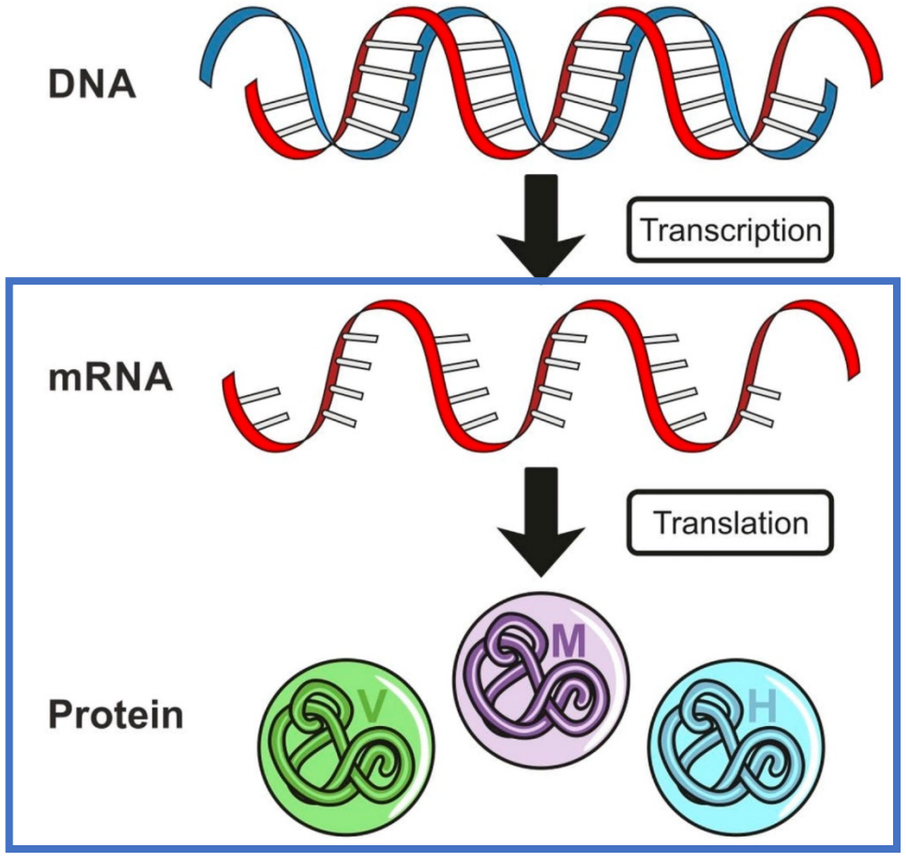
- **mRNA Vaccines**
  - Pfizer/BioNTech (BNT 162b2)
  - Moderna (mRNA-1273)
- **Viral-Vectored Vaccines**
  - Janssen/J&J (Ad26.COV2.S)
  - The AstraZeneca/Oxford vaccine (ChAdOx1 nCoV-19) is also a viral-vectored vaccine (uses a chimpanzee adenovirus) that has not yet filed for an EUA by the FDA, but is being used in Europe, the UK, and other countries

Coronavirus Structure



Because there is Strength in Unity

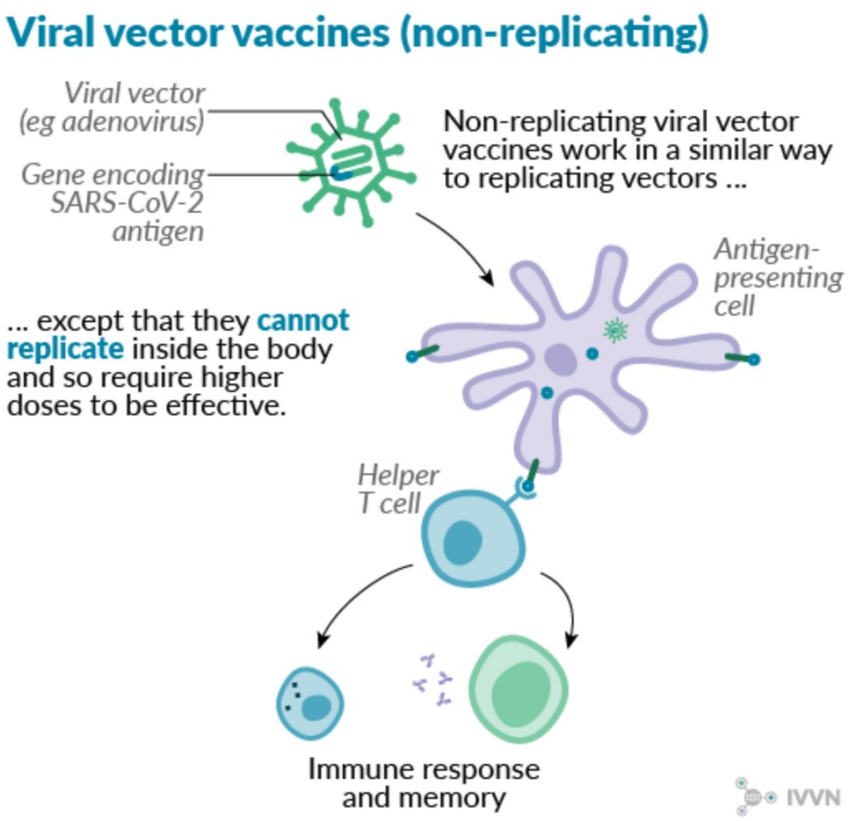
A Brief Review of Genetics



- In cellular organisms, the genetic code is carried in DNA
- DNA is **transcribed** into mRNA
- mRNA is then **translated** in the ribosomes to make proteins
- mRNA is rapidly degraded after being used by the ribosomes, and does not go back into the nucleus

Because there is Strength in Unity

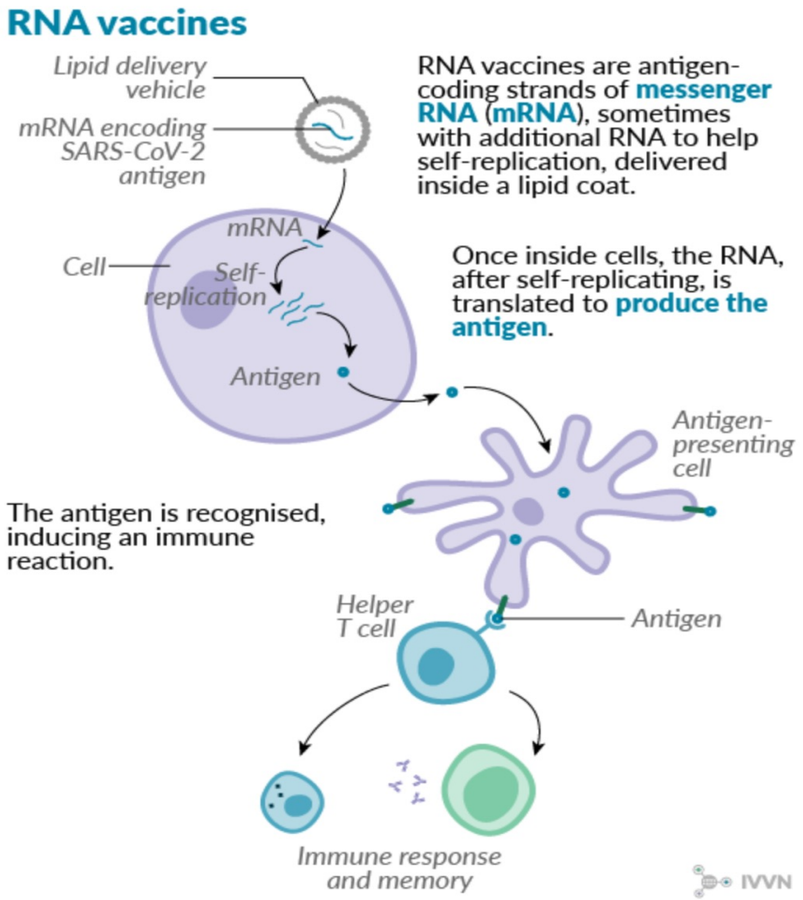
Non-replicating Viral Vector Vaccine



- The adenovirus vector is genetically modified to carry a gene for the SARS-CoV-2 spike protein (and made incapable of replication)
- Our own cells make the spike
- The spike protein provokes an immune response
- Immune response is both antibody and T cell
- Theoretical downside: immunity to adenovirus vector

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested

How do RNA vaccines work?



- mRNA is made that codes for the SARS-CoV-2 spike protein
- mRNA is packaged in lipid nanoparticles
- Inside cells, mRNA is used by ribosomes to make spike protein
- Immune system produces antibodies and T-cells targeted for spike protein

Because there is Strength in Unity

Current Viral-Vectored Vaccines in Use Around the World

1) Janssen/J&J – adenovirus 26

2) AstraZeneca/Oxford – simian (chimpanzee) adenovirus

3) Gamaleya (“Sputnik V”) – adenovirus 5 and 26

4) Cansino – adenovirus 5

ACIP Updates on Janssen Vaccine

Summary of 4-14-21 ACIP Emergency Meeting

Adenovirus vector vaccines

Adenovirus Vector

Janssen/J&J

AstraZeneca

Janssen

One dose
Human Adenovirus 26 vector
EUA in the US issued Feb 2021
EMA authorized for Europe
Doses not yet delivered/administered

AstraZeneca

Two doses
Chimp adenovirus vector
Awaiting EUA application in the US
Approved in UK, Europe

- Concerns for rare clotting events seen after COVID-19 adenovirus vector vaccines
- Clinical syndromes after both vaccines appear similar
- However, extent to which the cases seen after both adenovirus vector vaccines represent the same syndrome is unknown

EUA: Emergency Use Authorization; EMA: European Medicines Agency

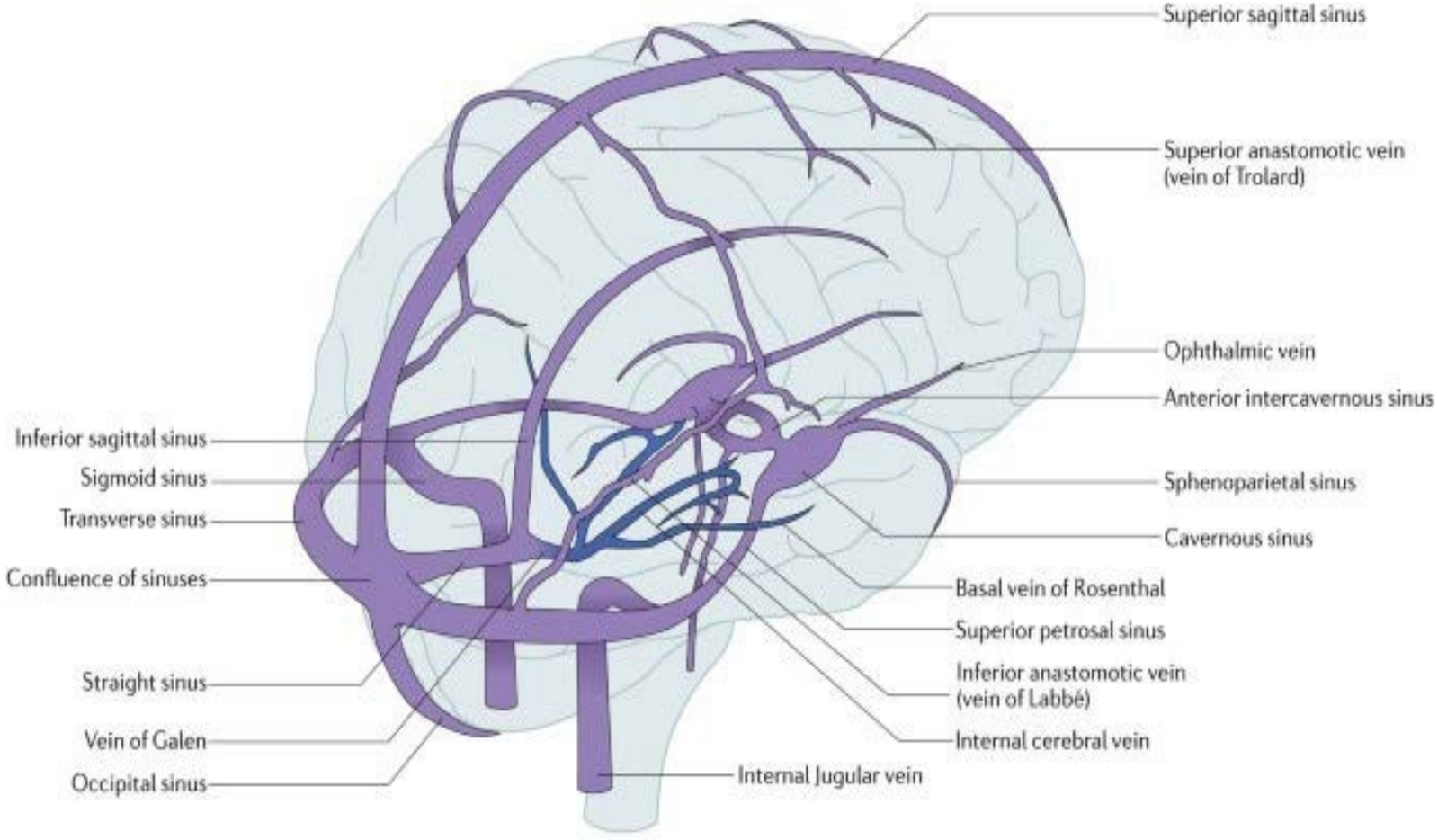
Platelets and thrombocytopenia (low platelets)*

- 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

Cerebral Venous Sinus Thrombosis (CVST) – a brief background

- Thrombosis (blood clots) within large vessels draining blood from the brain
- Symptoms typically include headache, nausea, vomiting, other neurologic symptoms
- Presentation acute →weeks, months



http://www.med.umich.edu%2F1libr%2FStroke%2FSinusVeinThrombosis.pdf&usg=AOvVaw3qjvm4UOFcHN-eR4O3Kyf8

Cerebral venous sinus thrombosis (CVST)

Background epidemiology[1-3]

- Rare, 0.22–1.57 per 100,000, ~0.5-1% of all strokes
- Median age 37 years
- 8% of patients >65 years
- Female:male ratio of 3:1

Risk factors[4]

- Prothrombotic conditions (genetic or acquired)
- Oral contraceptives
- Pregnancy and the post-partum period
- Malignancy
- Infection
- Mechanical precipitants (lumbar puncture)

1 Cerebral vein and dural sinus thrombosis in Portugal: 1980-1998. Ferro JM, Correia M, Pontes C, Baptista MV, Pita F, Cerebral Venous Thrombosis Portuguese Collaborative Study Group (Venoport) Cerebrovasc Dis. 2001;11(3):177. 2 The incidence of cerebral venous thrombosis: a cross-sectional study. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. Stroke. 2012 Dec;43(12):3375-7..

3 Cerebral Venous Sinus Thrombosis Incidence Is Higher Than Previously Thought: A Retrospective Population-Based Study. Devasagayam S, Wyatt B, Leyden J, Kleinig T. Stroke. 2016 Sep;47(9):2180-2.

4 Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Saposnik G, et al. 2011;42(4):1158.

AstraZeneca (AZ) vaccine

- Last week, EMA's safety committee (PRAC) released report concluding:
  - **Strong association** and **probable causal link** between the AZ vaccine and rare clotting events

From the European Union:

- 62 cases of CVST & 24 cases of splanchnic vein thrombosis with thrombocytopenia; 18 were fatal
- Most in females <60 years of age
- Within 2 weeks of AZ vaccine receipt
- Due to different ways vaccine used in each country, cannot exclude age/gender as risk factors

From the United Kingdom:

- 79 cases of thrombosis + thrombocytopenia; 19 were fatal
- 44 cases of CVST (14 fatalities) & 35 cases of other clots (5 fatalities)
- 51 cases were female; 28 were male
- 20.2 million doses given. Estimated risk ~4 per million pop. ('slightly higher incidence' in younger age groups)

CVST: Cerebral Venous Sinus Thrombosis

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.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

AstraZeneca (AZ) vaccine:

Recommendations for use

- EMA's Pharmacovigilance Risk Assessment Committee (PRAC) does not make vaccine policy for the EU; each country weighs the risks and benefits of AZ vaccine individually
- Many countries have adopted age-based recommendations
  - UK: Adults ≥30 years of age; April 7, 2021
  - Australia: Adults ≥50 years of age; April 8, 2021
  - European countries: Adults ≥55 to ≥70 years of age

EMA: European Medicines Agency

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
- Recommendations for Public Health: case reporting through VAERS
- Recommendations for the Public: clinical signs and symptoms to monitor

HAN Archive- 00442 | Health Alert Network (HAN) (cdc.gov)

Janssen/J&J COVID-19 vaccine:

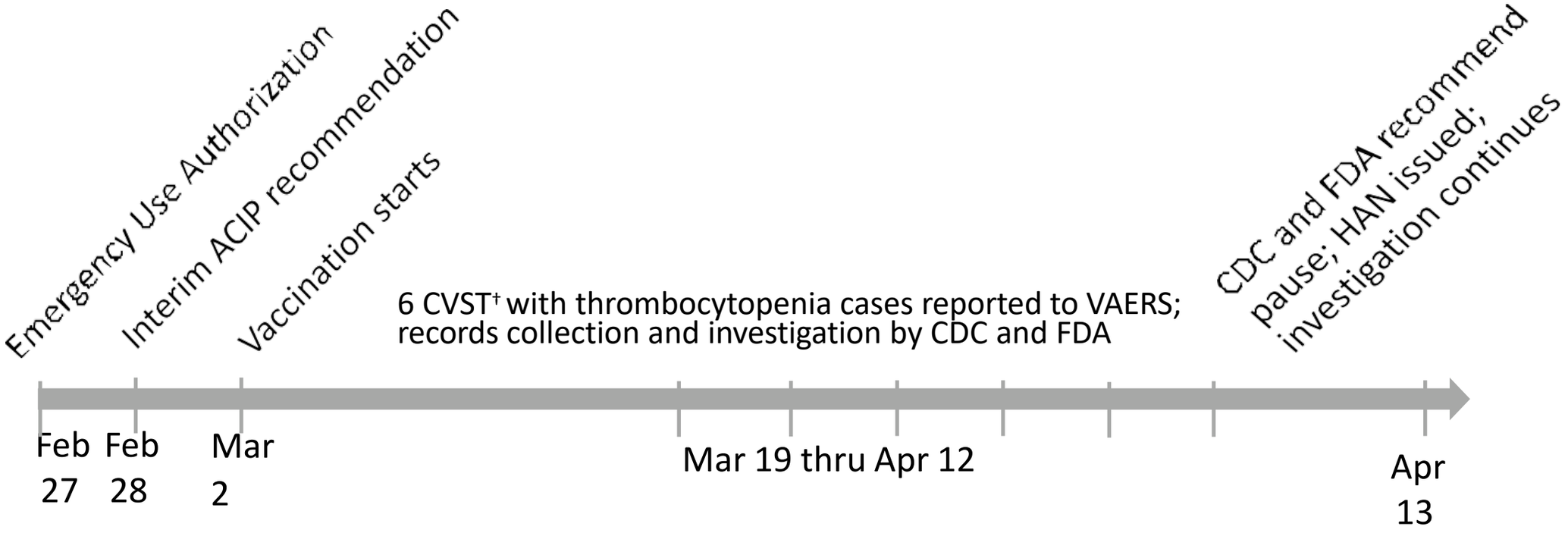
HAN released April 13, 2021

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

HAN Archive- 00442 | Health Alert Network (HAN) (cdc.gov)

Janssen COVID-19 vaccine timeline* (2021)



* For illustrative purposes, not drawn to scale, † cerebral venous sinus thrombosis

Detailed Case Description As of 14 Apr 2021

SOURCE	CASE	CIOMS #	SERIOUS ADVERSE EVENT	RISK FACTOR(S)	PLATELET COUNT	COVID STATUS	TTO	Treatment	Status
CLINICAL TRIAL CASES									
Study 3001	25 YO Male on Vaccine	**20201017267**	CVST with hemorrhage	Stenosis of transverse sinus, URI suspected	64,000 (Anti-PF4+)	Negative	8 days	Heparin TPA and platelets, angioplasty and thrombectomies	Recovered
Study 3001	24 YO female on **placebo**	**20210202793**	CVST	Newly prescribed OCP	Normal (Anti-PF4-)	Negative	>50 days	N/A	Recovered
POST-AUTHORIZATION CASES									
VAERS # 1114806	45 YO female	**20210354798**	CVST with hemorrhage	none	"thrombocytopenia"	Unknown	11 days	Unknown	Fatal
VAERS 1133212	38 YO female	**20210408478**	CVST	Unknown	Unknown	Unknown	10-14 days	Heparin	Not Recovered at this time
VAERS #1141160-1	59 YO Female	**20210407977**	Extensive DVTs	Coronary artery disease	15,000	Unknown	7 days	Vena cava filter- IVC, thrombectomy	Not Recovered at this time
Janssen SAE Nevada	18 YO female	**20210407314**	CVST with hemorrhage	unknown	16,000	Unknown	14 days	Heparin then switched to "British guidelines" and thrombectomy	Not Recovered at this time
Janssen SAE (NEJM -editor notification) Nebraska	48 YO female	**20210415297**	TTP, splanchnic veins thrombosis, CVST, then given heparin and then additional hepatic and splanchnic vein thrombosis	Unknown	<13,000 (hi d-dimer, Anti-PF4+)	Negative	14 days	Heparin first and switched to argatroban then IVIG	Not Recovered at this time
Janssen SAE NJ/PA	26 YO female	**20210416236**	CVST, PE, portal vein thrombosis	Obesity	120,000 (hi d-dimer, Anti-PF4+)	Negative	7 days	Heparin and then IVIG	Discharged from hospital
VAERS 1182133	28 YO female	**In processing**	Details pending, FOI requested						

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/mm3) 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 (150–450K/mm3)

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

Characteristics of patients with CVST and thrombocytopenia* after Janssen COVID-19 vaccine, N=6

- Median age 33 years (range 18–48)
- Median time to symptom onset 8 days (range 6–13 days)
- All cases occurred in white females
- Current estrogen/progesterone use (n=1)
- Pregnant or post-partum (n=0)
- Pre-existing conditions
  - Obesity (n=3)
  - Hypothyroidism (n=1)
  - Hypertension (n=1)
  - Asthma (n=1)
  - Coagulation disorders (none known)

* Note: Thrombosis usually does not occur in the presence of low platelets; these case presentations are atypical and consistent with cases observed after AstraZeneca COVID-19 vaccine

Initial and late signs and symptoms among CVST patients*
(patients listed in no particular order)

	Initial features	Late features
Patient 1	Headaches, lethargy	Severe headache, left-sided weakness, vomiting
Patient 2	Headaches	Severe headache, aphasia
Patient 3	Headaches, vomiting, fever	Left arm weakness, right gaze deviation, left neglect
Patient 4	Headaches, chills, myalgias	Severe abdominal pain and fever
Patient 5	Headache, chills, dyspnea, fever	Bruising, unilateral leg swelling, loss of consciousness
Patient 6	Back pain, bruising	Headache, abdominal pain

*** All were hospitalized and admitted to ICU**

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)

Key Messages For Clinicians (1)

- Maintain a high index of suspicion for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the Jansen COVID-19 vaccine, including severe headache, backache, new neurologic symptoms, severe abdominal pain, shortness of breath, leg swelling, petechiae (tiny red spots on the skin), or new or easy bruising. Obtain platelet counts and screen for evidence of immune thrombotic thrombocytopenia.
- In patients with a thrombotic event and thrombocytopenia after the Jansen COVID-19 vaccine, evaluate initially with a screening PF4 enzyme-linked immunosorbent (ELISA) assay as would be performed for autoimmune HIT. Consultation with a hematologist is strongly recommended.

Key Messages For Clinicians (2)

- Do not treat patients with thrombotic events and thrombocytopenia following receipt of Janssen COVID-19 vaccine with heparin, unless HIT testing is negative.
- If HIT testing is positive or unable to be performed in patient with thrombotic events and thrombocytopenia following receipt of Jansen COVID-19 vaccine, non-heparin anticoagulants and high-dose intravenous immune globulin should be strongly considered.
- Report adverse events to VAERS, including serious and life-threatening adverse events and deaths in patients following receipt of COVID-19 vaccines as required under the Emergency Use Authorizations for COVID-19 vaccines.

Key Messages

- **For public health**
  - 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 as required under the EUAs for COVID-19 vaccines.
  - Disseminate information to healthcare providers in your jurisdictions.

- **For the public**
  - If you have received the Janssen COVID-19 vaccine and develop severe headache, abdominal pain, leg pain, or shortness of breath within three weeks after vaccination, contact your healthcare provider, or seek medical care.
  - Report adverse events following receipt of any COVID-19 vaccine to VAERS.
  - If you are scheduled to receive the Janssen vaccine, please contact your healthcare provider, vaccination location, or clinic to learn about additional vaccine availability.

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

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
- **Type "IHS" in Box 26**

- HIPAA permits reporting of protected health information to public health authorities including CDC and FDA

What is known so far

- Thrombocytopenic thrombotic events after the AstraZeneca vaccine have occurred
- In the US, 6 cases of CVST reported after receipt of the Janssen COVID-19 vaccine.
- No cases of CVST with thrombocytopenia reported after receipt of either Pfizer and Moderna COVID-19 vaccines
- CVST cases have occurred primarily in younger adults, females
- CVST can be clinically devastating or fatal
- In the US, alternative COVID-19 vaccines (mRNA vaccines) are available
  - Based on current projections, supply of both mRNA vaccines fairly stable for near future

CVST: Cerebral Venous Sinus Thrombosis

What we do NOT know

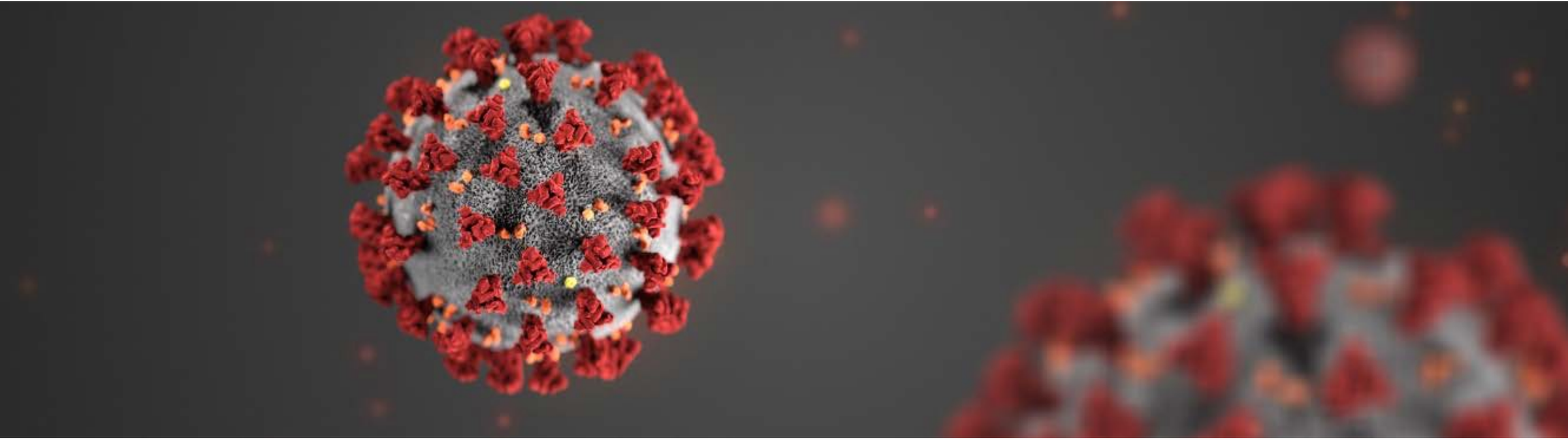
- True background incidence of CVST with thrombocytopenia
- Specific risk factors for thrombocytopenic thrombotic events
- Incidence of other thrombotic (non-CVST) cases with thrombocytopenia after Janssen vaccine
- Ability to compare or generalize thrombotic cases after the AstraZeneca vaccine to Janssen vaccine
- True incidence of thrombocytopenic thrombotic events/CVST after a Janssen/J&J COVID-19 vaccine
  - More cases may be identified in the coming days/weeks

CVST: Cerebral Venous Sinus Thrombosis

ACIP Conclusion

- Not enough data to make a decision to withdraw the Janssen/J&J COVID-19 vaccine completely
- Risk of continuing to use the Janssen/J&J COVID-19 vaccine appears to outweigh the benefit in the immediate short term
- Decision to continue to pause use of the Janssen vaccine for 7-10 days to allow time to:
  - Assess the true incidence of thrombocytopenic thrombotic events/CVST after a Janssen/J&J COVID-19 vaccine
  - Provide more time for clinicians to become aware of the diagnosis and management of these potential complications

CVST: Cerebral Venous Sinus Thrombosis



Thank you!

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 or Indian Health Service.