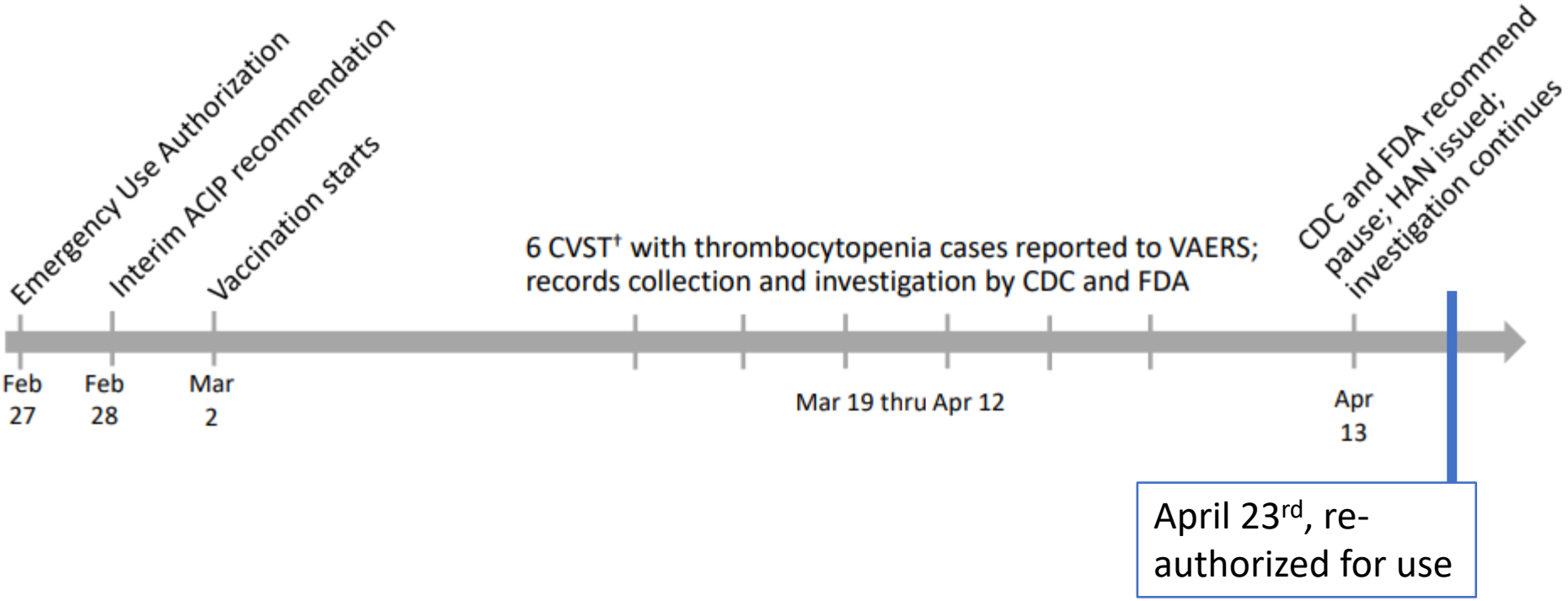
Janssen COVID-19 vaccine timeline* (2021)



For clinicians

- 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.
- 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 Takeaways
Thrombosis with Thrombocytopenia Syndrome (TTS)

- **Diagnosis** (must meet all four criteria):

    1. COVID vaccine (Johnson & Johnson/AstraZeneca *only* to date) 4 to 30 days previously
    2. Venous or arterial thrombosis (often cerebral or abdominal)
    3. Thrombocytopenia*
    4. Positive PF4 "HIT" (heparin-induced thrombocytopenia) ELISA

- **Incidence is extremely rare**. Risk of death and serious outcome of COVID-19, including thrombosis, far outweigh risk of TTS possibly associated with highly efficacious vaccines.
- **Urgent medical evaluation for TTS** is indicated if any of the following develop 4 to 30 days after vaccination:
    - Severe headache
    - Visual changes
    - Abdominal pain
    - Nausea and vomiting
    - Back pain
    - Shortness of breath
    - Leg pain or swelling
    - Petechiae, easy bruising, or bleeding

https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia

- **If TTS is suspected**, perform **immediate CBC with platelet count** and imaging for thrombosis based on symptoms.
- If thrombocytopenia or thrombosis are present, recommend urgent consultation from hematologist with expertise in hemostasis. ***Avoid use of heparin until TTS has been ruled out or until an alternative other plausible diagnosis has been made***.
- **Initial work-up (a normal platelet count is less concerning for TTS*):**
  - CBC ***with platelet count*** and peripheral smear
  - Imaging for thrombosis based on signs/symptoms
  - PF4-ELISA (HIT assay); ***draw blood prior to any therapies***
  - Fibrinogen and D-dimers

- **Initiate therapy** with intravenous immune immunoglobin and nonheparin anticoagulation pending PF4 ELISA results if:
  - Signs/symptoms of serious thrombosis *AND* at least one of the following
    - Positive imaging *OR*
    - Low platelets* *OR*
    - Both

If PF4 ELISA returns negative and there is no thrombocytopenia, TTS is ruled out; treat as standard venous thromboembolism.

OR

https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia

OR

- No signs, symptoms or imaging documenting thrombosis BUT
  - Low platelets *AND*
  - Very high or rising D-dimer OR positive PF4 ELISA
- If thrombocytopenia but no thrombosis and negative PF4 ELISA, likely ITP, see Q4
- Avoid platelet transfusions unless other treatments have been initiated AND life-threatening bleeding or imminent surgery
- Consider referral to tertiary care center if TTS is confirmed.

TTS is an evolving disorder, and updates will be made as new data become available.

***A patient who presents with thrombosis and a normal platelet count post-vaccination might be in an early stage of TTS.** Continued assessment for development of thrombocytopenia/TTS required. Use of non-heparin anticoagulant may be indicated if patient is 4 to 30 days post-Johnson & Johnson or AstraZeneca vaccine.

https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia

Cerebral venous sinus anatomy

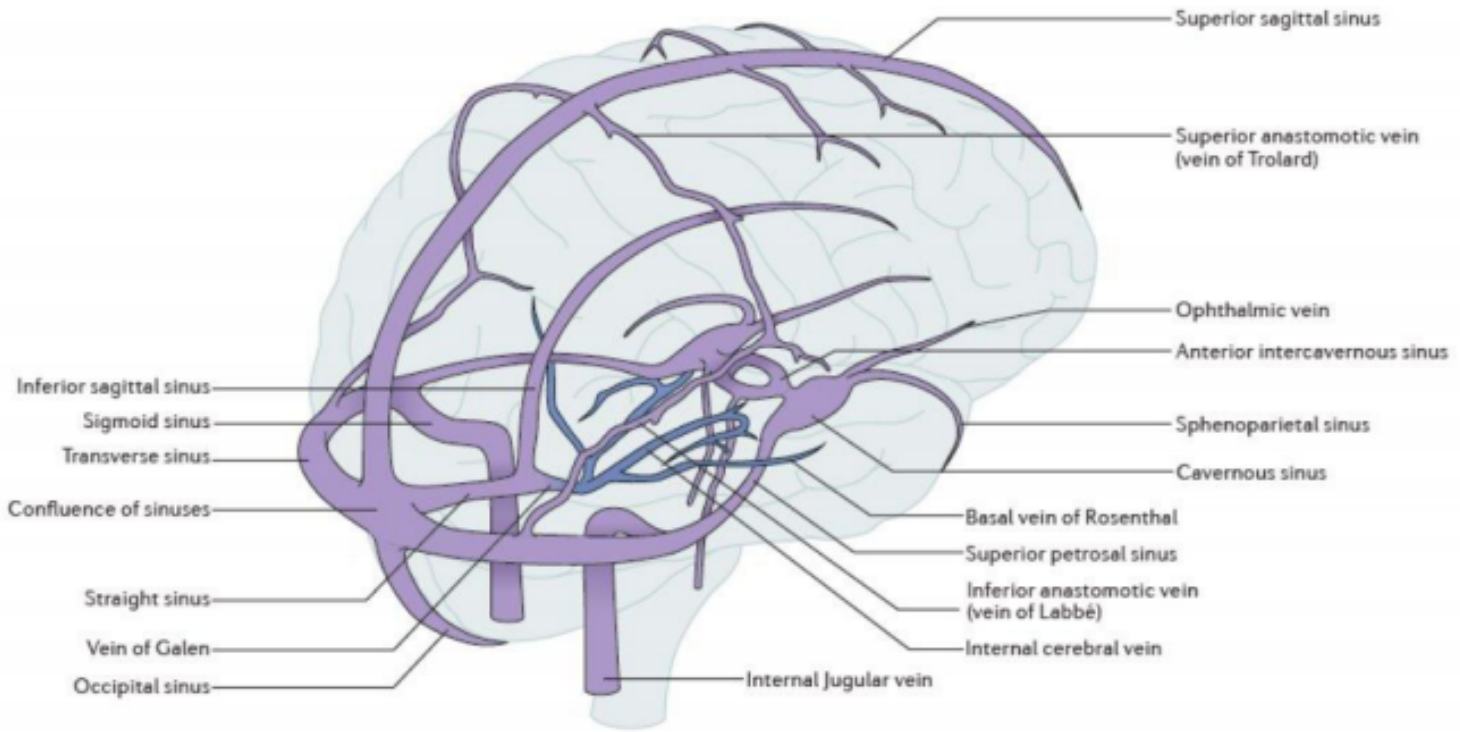


Figure 1 | **Anatomy of the cerebral venous system.** Diagram showing the main components of the cerebral venous system. Blue vessels represent the deep venous system.

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

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)

CVST signs and symptoms

- More common presentations
  - Isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema, and visual problems)
  - Focal syndrome (focal deficits, seizures, or both)
  - Encephalopathy (multifocal signs, mental status changes, stupor, or coma)

- Rare presentations
  - Cavernous sinus syndrome
  - Subarachnoid hemorrhage
  - Cranial nerve palsies

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

Observed vs. expected CVST cases following Janssen COVID-19 vaccine

- Estimated annual incidence of CVST ~0.5–2 cases per 100,000 population*
- Assumed risk period of 5.6% of a calendar year: (41 days/2) ÷ 365 days
- Doses administered among women aged 20–50 years = 1,402,712 doses (as of Apr 12)

Est. annual background incidence	Obs. cases in women aged 20–50 yrs	Exp. cases in women aged 20–50 yrs	Reporting ratio, women aged 20–50 yrs
0.5 per 100K	6	0.39	**15.4**
1.0 per 100K	6	0.79	**7.6**
1.5 per 100k	6	1.18	**5.1**
2.0 per 100k	6	1.58	**3.8**

* https://www.hopkinsmedicine.org/health/conditions-and-diseases/cerebral-venous-sinus-thrombosis, http://www.med.umich.edu/1libr/Stroke/SinusVeinThrombosis.pdf, https://www.nejm.org/doi/10.1056/NEJMra042354?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub, https://www.ahajournals.org/doi/pdf/10.1161/STROKEAHA.116.013617, https://www.nature.com/articles/nrneurol.2017.104

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

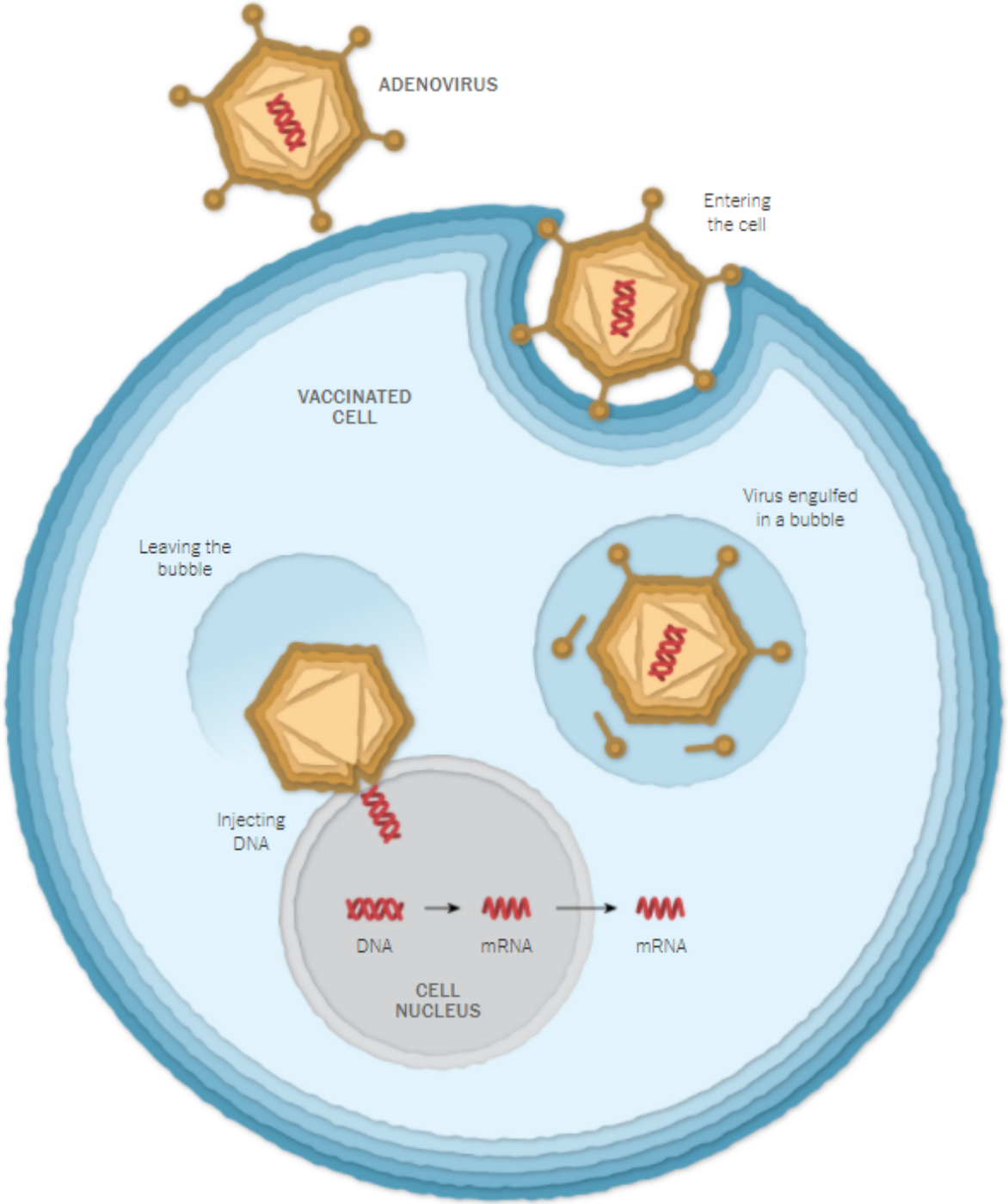
  video instructions
  https://youtu.be/sbCWhcQADFE

- 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

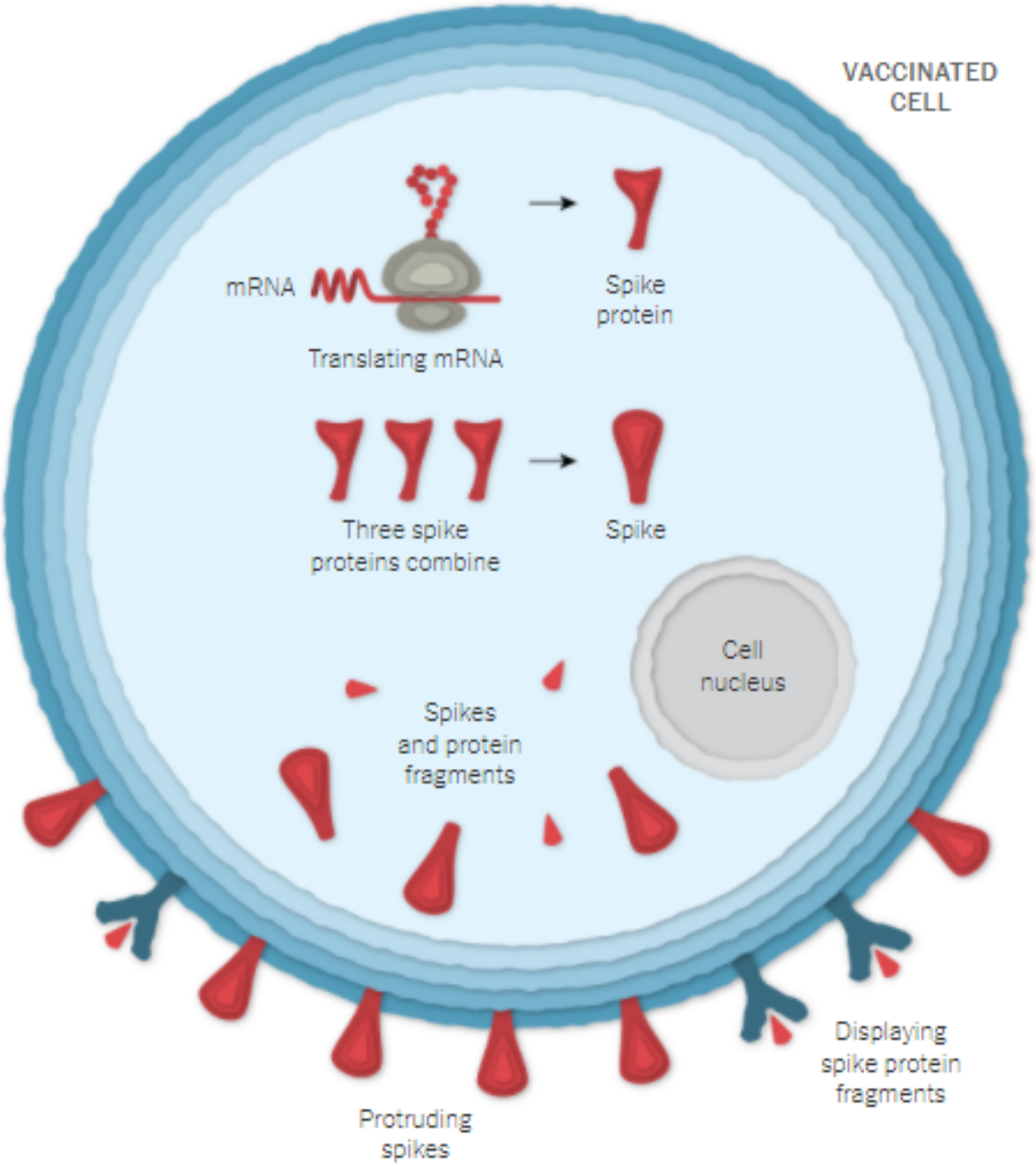
HOW DIFFERENT VACCINES WORK

AN UNOFFICIAL STAR WARS EXPLANATION

https://www.wpp.com/featured/work/supporting-the-roll-out-of-covid-19-vaccines



The New York Times



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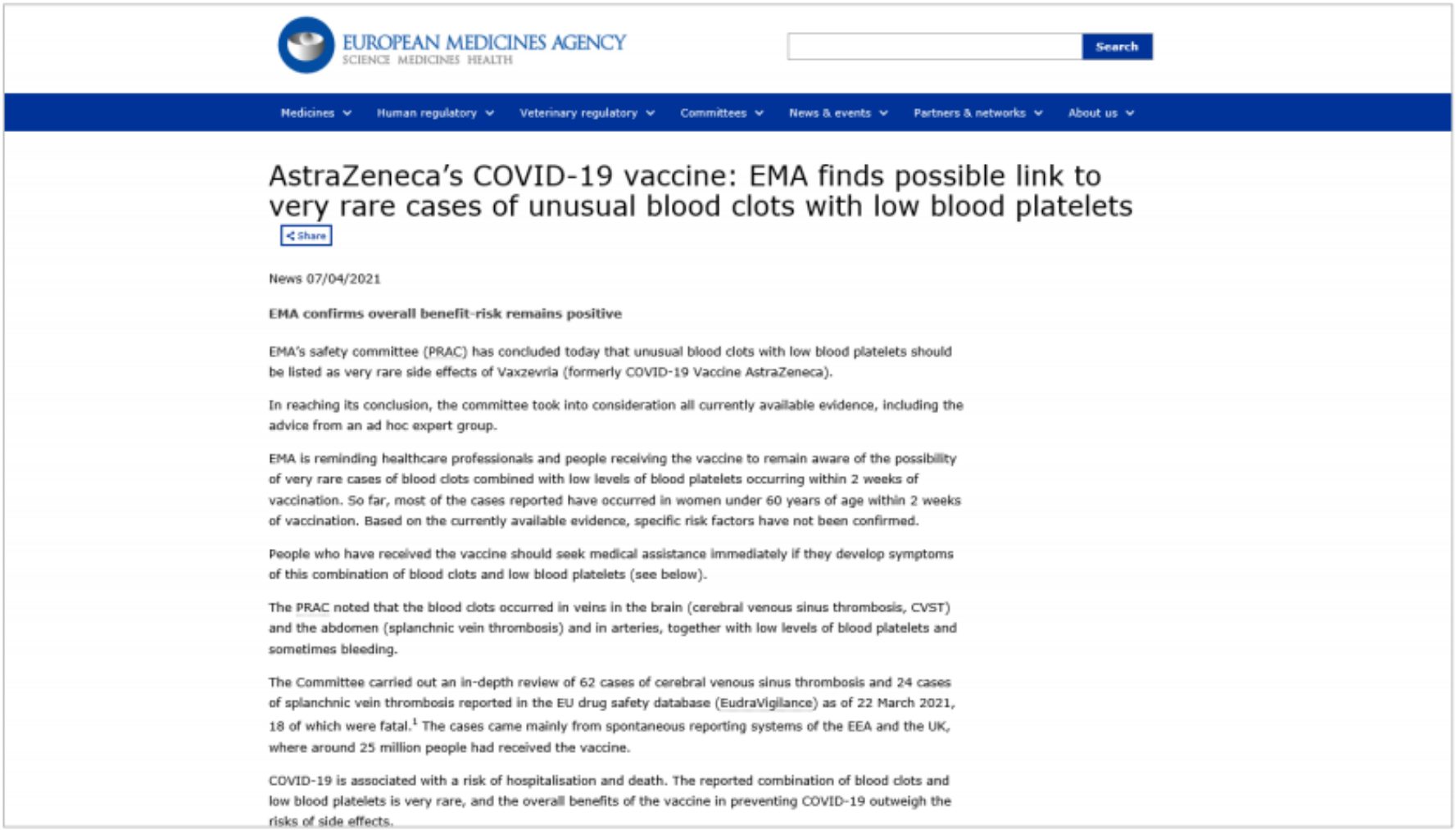

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AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets

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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

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