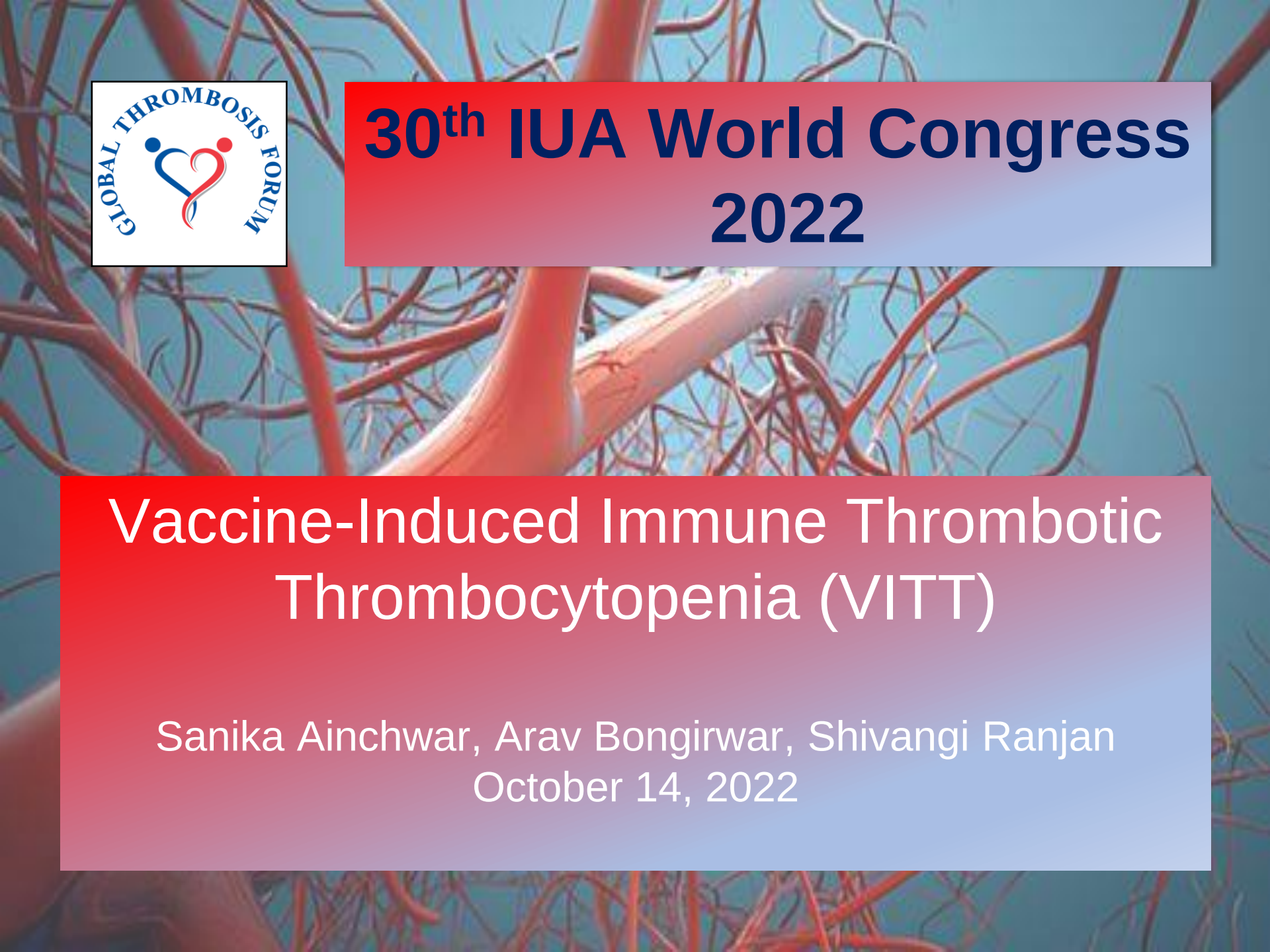

30th IUA World Congress 2022

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

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Abstract

In the midst of battling the COVID-19 pandemic, scientists created multiple different vaccines to prevent widespread COVID-19 infections. Unfortunately, 2 vaccines (AstraZeneca and Johnson and Johnson, J&J) resulted in some serious complications, such as the very rare condition of Vaccine-Induced Thrombotic Thrombocytopenia (VITT) which results in multiple thrombotic events all over the body, and Cerebral Venous Sinus Thrombosis (CVST). VITT is very similar to the thrombotic events produced by heparin in a condition called Heparin-Induced Thrombotic Thrombocytopenia (HITT).

We have attempted to research the cause, pathophysiology, and the management of VITT.

Introduction

- Covid-19, caused by a SARS-CoV-2 virus, has caused a significant worldwide scare and mortality. In March 2020, the WHO declared the COVID-19 infestation a pandemic.
- There was great motivation and pressure on global scientists to quickly develop a vaccine, and they succeeded by the development of the mRNA (the Moderna and BioNTech Pfizer), AstraZeneca, and J&J vaccines.
- Everything with the mRNA vaccines looked safe. Unfortunately, soon after the development of the AstraZeneca and J&J vaccines, a very serious but rare complication developed, involving thrombotic events and acute thrombocytopenia.

Introduction (cont'd)

- This condition was new, and scientists were quick to call it vaccine-induced immune thrombotic thrombocytopenia (VITT) and vaccine-induced prothrombotic immune thrombocytopenia in light of published cases and case reports in Israel, Norway, Germany, and the United Kingdom.
- VITT is an autoimmune disorder, in which the body produces antibodies that are harmful. This condition mimics heparin-induced thrombotic thrombocytopenia (HITT), yet it does not require heparin as a trigger.
- Acquired Thrombotic Thrombocytopenic Purpura, another rare condition, was reported by scientists in Israel, associated with BNT162b2 vaccine (BioNTech Pfizer vaccine).
- Today we are going to present our research on VITT because the condition, although very rare, could have a significant impact on the health of human beings.

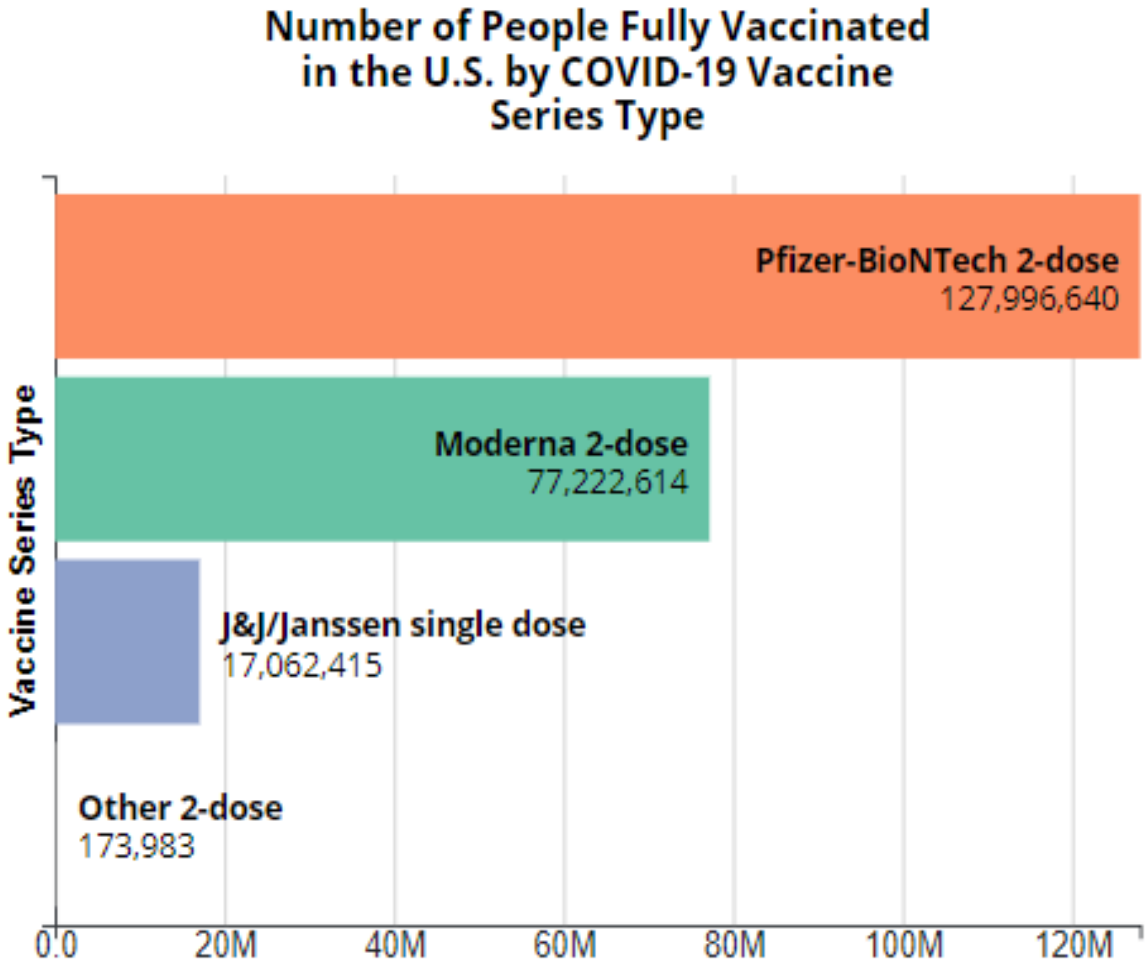
History of the Development of the COVID-19 Vaccine

- December 11, 2020: Pfizer-BioNTech was approved for use in humans by the Food and Drug Administration (FDA).
- December 18, 2020: Moderna was approved for use in humans by the FDA.
- February 27, 2021: J&J vaccine was approved for use in humans by the FDA.
- It should be noted that as of now, the AstraZeneca vaccine has not yet been approved for use in the U.S.

As of August 13th:

- The number of fully vaccinated people worldwide: 4,895,396,794

As of August 13th:



The History of VITT

FIRST CASE OF VITT

2021: Norway and Germany observed the first case of VITT following administration of the AstraZeneca vaccine.

NAMING

February 2021: The term VITT was coined by the scientists as a rare adverse event following adenoviral vector-based vaccinations for COVID-19 (Astra-Zeneca). VITT results in thrombosis, especially of the cerebral and splanchnic vasculature.

J&J VACCINE IN THE US

April 2021: the first case of VITT in the US was discovered in a male, age <50 years, and developed symptoms (pain in the toes, thighs, and chest) 10 days following the administration.

INITIAL PREVALENCE OF FEMALE PATIENTS

Initially, more VITT cases were seen in women, since more women were health workers. However, this trend is not seen now in the general population.

CURRENT CASES

September 2022: There have been over 60 recorded cases of VITT in the US.

Cerebral Venous Sinus Thrombosis (CVST)

- The Pharmacovigilance Risk Assessment Committee (PRAC) from the European Medicines Agency (EMA) noted that blood clots had occurred in veins in the brain causing CVST and the abdomen (splanchnic vein thrombosis) and in arteries, together with low levels of platelets and sometimes bleeding.
- The PRAC carried out an in-depth review of 62 cases of CVST and 24 cases of splanchnic vein thrombosis reported in the EU drug safety database (EudraVigilance). As of 22 March 2021, 18 of these cases were fatal.
- The EMA safety committee (PRAC) found a possible link to very rare cases of unusual blood clots with low blood platelets following the AstraZeneca vaccine.
- April 23, 2021: CVST and Thrombocytopenia Syndrome (TTS) following J&J COVID-19 vaccine were reported by the Advisory Committee on Immunization Practices (ACIP).

CVST Cases Following COVID-19 Vaccines

Vaccines Administered	CVST cases following COVID-19 Vaccines	Platelet Counts	Doses administered (in millions)
J&J Vaccine	6	<150,000	6.86
Moderna Vaccine	3	150,000-450,000	84.7
Pfizer Vaccine	0	<150,000	97.9

The Incidence of VITT

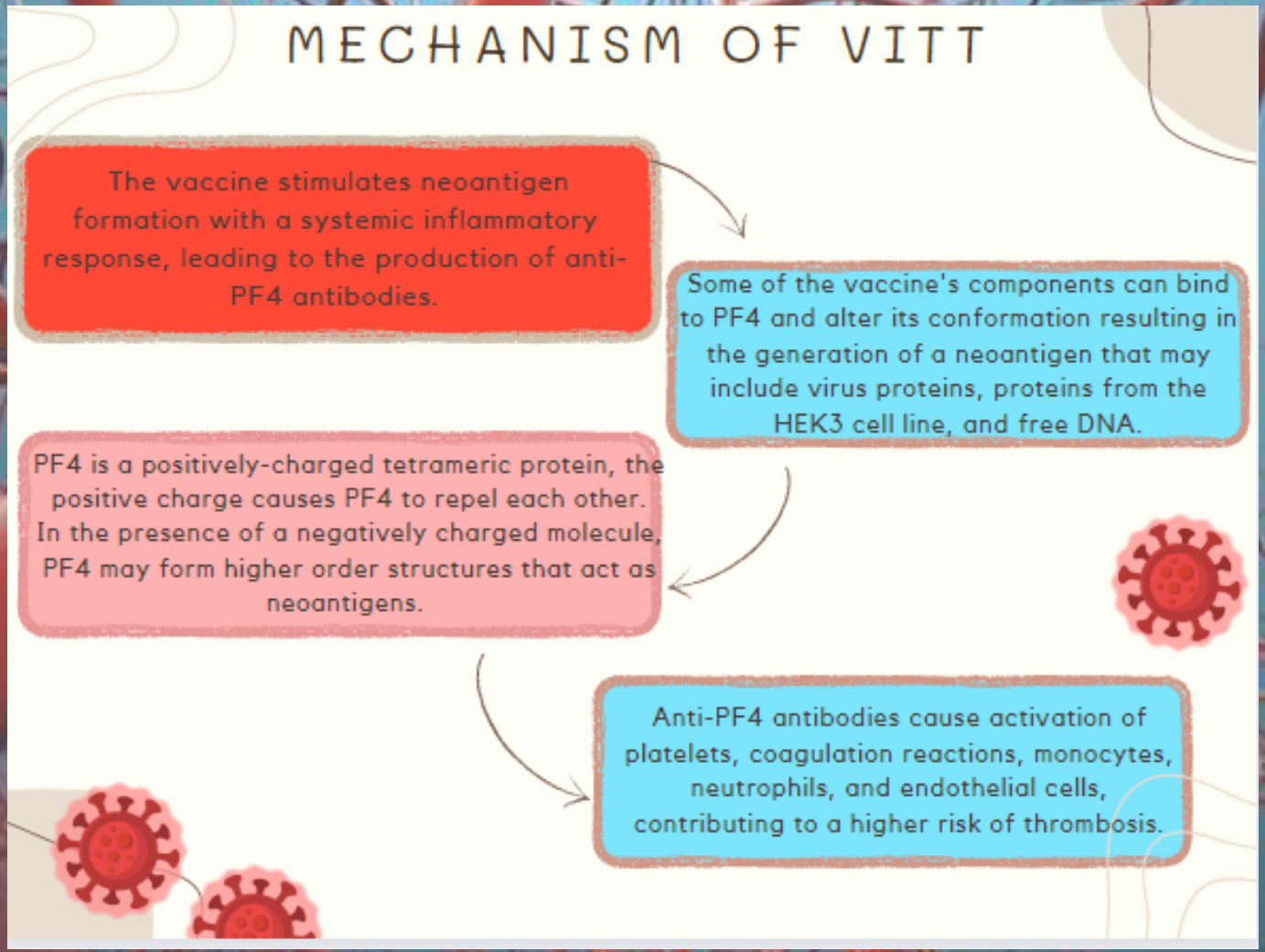
- The incidence of VITT following vaccination seems to be incredibly low, approximately 3.8 cases per million in the US.

- Due to tens of millions of vaccinated individuals, around 60 people have been affected, and this makes scientists very nervous.

Pathophysiology of VITT

- VITT is caused by antibodies that recognize platelet factor 4 bound to platelets.
- The antibodies are immunoglobulin G (IgG) molecules that activate platelets via low affinity platelet Fcγlla receptors.
- The platelet activation results in stimulation of the coagulation system and clinically significant thromboembolic complications.
- VITT antibodies are detectable in PF4/polyanion and PF4 enzyme-linked immunosorbent assay (ELISA) and in functional assays.
- The antibodies are not heparin dependent.

Steps in Antibody Formation

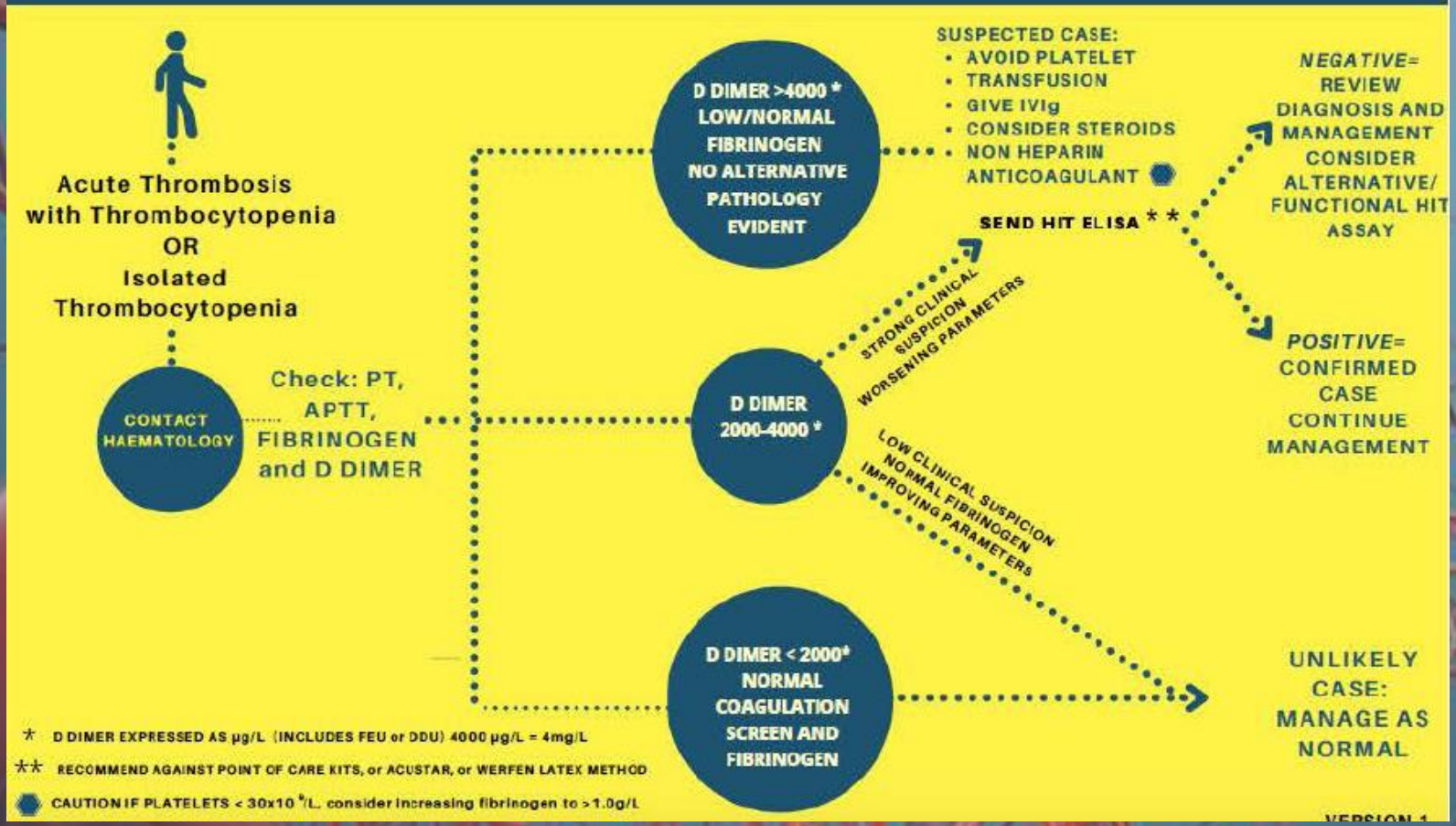


Mechanism of VITT

- VITT can occur in typical sites of venous thromboembolism such as pulmonary embolism (PE) or deep vein thrombosis (DVT) in the leg; however, a distinctive feature of the syndrome is thrombosis in unusual sites including the splanchnic (splenic, portal, mesenteric) veins, adrenal veins (causing risk for adrenal failure), and the cerebral and ophthalmic veins.
- Arterial thrombosis including ischemic stroke (in middle cerebral artery) and peripheral arterial occlusion has also occurred, often in individuals with venous thrombosis.

Investigation of Vaccine Associated Thrombosis and Thrombocytopenia

DAY 5-30 POST-VACCINATION



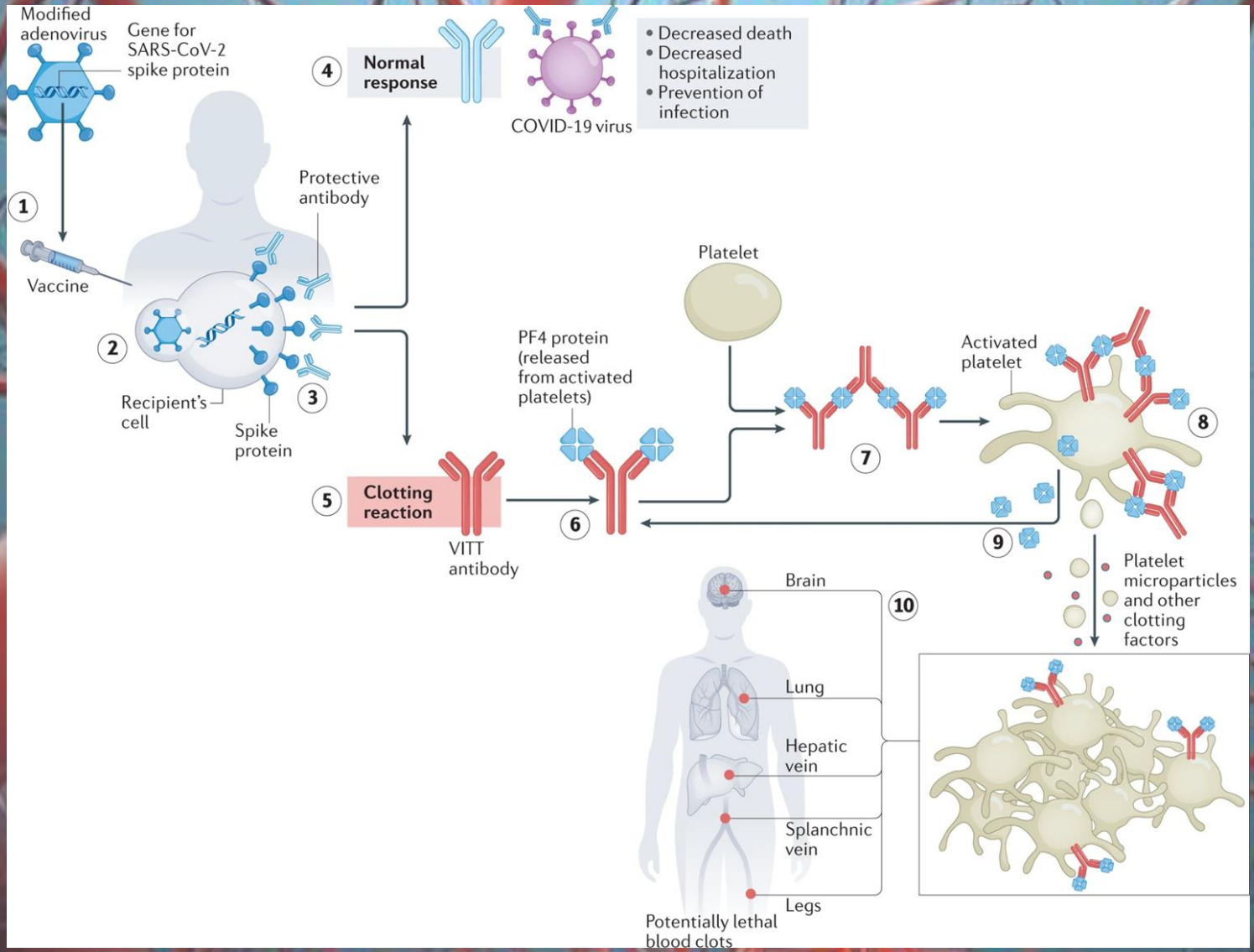
Role of the Immune System

Steps 1-4: In most people, administration of an adenovirus-based COVID-19 vaccine induces antibodies to the spike protein of SARS-CoV-2 and protects the recipient against COVID-19.

Steps 5-7: In rare cases, VITT antibodies are induced that can bind to platelet factor 4 (PF4) and form immune complexes that activate platelets.

Steps 8-10: This leads to pathological activation of clotting cascades and a fall in platelet counts. VITT-associated clots have been described in the brains, lungs, abdomen, liver and legs.

VITT


Modified adenovirus
Gene for SARS-CoV-2 spike protein
1
Vaccine
2
Recipient's cell
3
Spike protein
Protective antibody
4
Normal response
COVID-19 virus
• Decreased death
• Decreased hospitalization
• Prevention of infection
5
Clotting reaction
VITT antibody
PF4 protein (released from activated platelets)
6
Platelet
7
Activated platelet
8
9
Platelet microparticles and other clotting factors
10
Brain
Lung
Hepatic vein
Splanchnic vein
Legs
Potentially lethal blood clots

Are Certain People More Likely to get VITT?

- We do not know if certain patients are more likely to get VITT.
- We do not have any evidence that VITT is more common in people who have had blood clots before, people with a family history of blood clots, people on birth control or other hormones, people with autoimmune disease, people with low platelets or other platelet disorders, or pregnant people, because VITT does not develop through the same process as more common types of bleeding or clotting problems.
- It may be possible, that people with a history of HITT, or CVST with low platelets are at increased risk of VITT.
- Such people should receive an mRNA vaccine (Pfizer or Moderna) rather than an adenoviral vector vaccine.

When Should I Suspect My Patient has VITT?

- Any patient with unusual symptoms following vaccination should be assessed by a health care provider.
- Some symptoms make it more likely that a patient has VITT (persistent and severe headache; focal neurological symptoms, including blurred or double vision); shortness of breath; chest, back, or abdominal pain; unusual bleeding, bruising, petechiae, or blood blisters; swelling and redness in a limb; or pallor and coldness in a limb.
- VITT seems to occur between 4-28 days post vaccination. Symptoms that begin in this time frame should raise the clinical suspicion of VITT.
- Patients with symptoms (listed in Appendix) suspicious of VITT should urgently seek care at their nearest emergency department.

Diagnosis of VITT

Patient must meet all five of the following criteria to be diagnosed with VITT:

- COVID vaccine was administered 4 to 28 days prior to symptom onset.
- Venous or arterial thrombosis (often cerebral or abdominal).
- Thrombocytopenia (platelet count < 150 x 109/L).
- Positive PF4-ELISA (HIT assay).
- Markedly elevated D-dimer (> 4 times upper limit of normal).

Management/Prevention of VITT

Management of VITT is similar to that of severe HITT in patients:

- IV Immunoglobulin (IVIG) 1 g/kg daily for two days.
- Non-heparin anticoagulation.
- Parenteral direct thrombin inhibitors (argatroban or bivalrudin), *OR*
- Direct oral anticoagulants without lead-in heparin phase. First line: DOAC's:
  - Direct Factor Xa inhibitors: apixaban, edoxaban or rivaroxaban.
  - Dose is identical to the dose used to treat uncomplicated deep vein thrombosis.

Management/Prevention of VITT (cont'd)

- In cases of renal impairment, use of apixaban is recommended.
- In pregnant and lactating patients with presumptive or confirmed VITT, direct oral factor Xa inhibitors are not recommended.
- Fondaparinux, OR
- Danaparoid.

Avoid the following:

- Heparin.
- Platelet transfusions.
- Aspirin as either treatment or prophylaxis for VITT
- Additional therapies: Plasma exchange.
- Most effective method of prevention is, of course, to not take the J&J vaccine.

Complications of VITT

Because VITT causes a systemic response in the body, it can affect multiple organs and lead to fatality, or any of the following:

- Ischemic stroke.
- Myocardial infarction.
- Pulmonary embolism.
- Serious bleeding.
- Sudden death.

Is VITT and HITT same?

VITT is very similar to HITT, the only difference being that the condition is caused following the administration of a vaccine.

Can Patients Who Develop VITT Safely Receive a 2nd Dose of the Same Vaccine?

- Patients who have experienced major venous or arterial thrombosis with thrombocytopenia following vaccination with the AstraZeneca/COVISHIELD COVID19 vaccine or the J&J vaccine should not receive a second dose of either of these vaccines.

- A second dose of mRNA-based COVID-19 vaccines may be safe.

Further Development

- Further characterization of mechanism of development of VITT.
- Duration of anticoagulation.
- Develop strategies to prevent platelet activation.

Conclusion

- In conclusion, VITT is an extremely rare but very serious autoimmune disorder in which the body produces antibodies in reaction to adenoviral vaccines (e.g. J&J and AstraZeneca vaccines).
- VITT is also very similar to HITT in terms of its mechanism. VITT is caused by immunoglobulin that recognizes PF4 bound to platelets. It is characterized by a significant drop in platelet count, shortness of breath, chest pain, and swelling in the leg.
- For treatment, one should avoid heparin and be treated with DOACs.
- Although there is significant fear within the community due to VITT in reaction to the J&J vaccine, we strongly recommend people to take the COVID-19 vaccines (Moderna and Pfizer) due to how low the incidence of VITT is. Acquired Thrombotic Thrombocytopenic Purpura: a rare disease associated with BNT162b2 vaccine was also reported by scientists in Israel.

Acknowledgments

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Appendix - Patients Should Seek Medical Assistance Immediately if the Following Occurs

- Shortness of breath.
- Chest pain.
- Swelling in the leg.
- Persistent abdominal pain.
- Neurological symptoms, including severe and persistent headaches or blurred vision.
- Tiny blood spots under the skin beyond the site of injection.