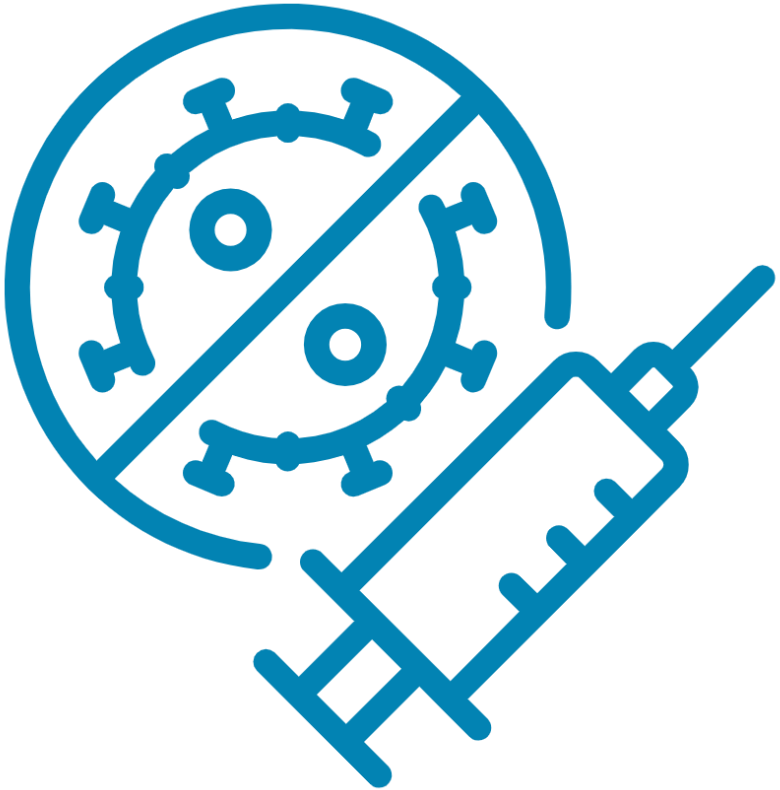
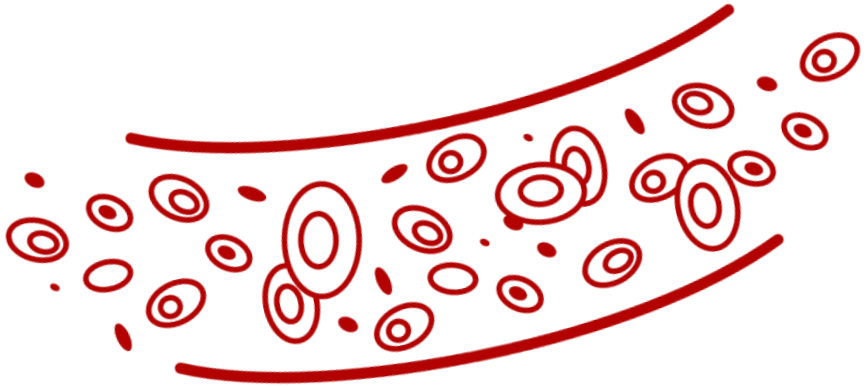
2021/8/1 Sysmex webinar

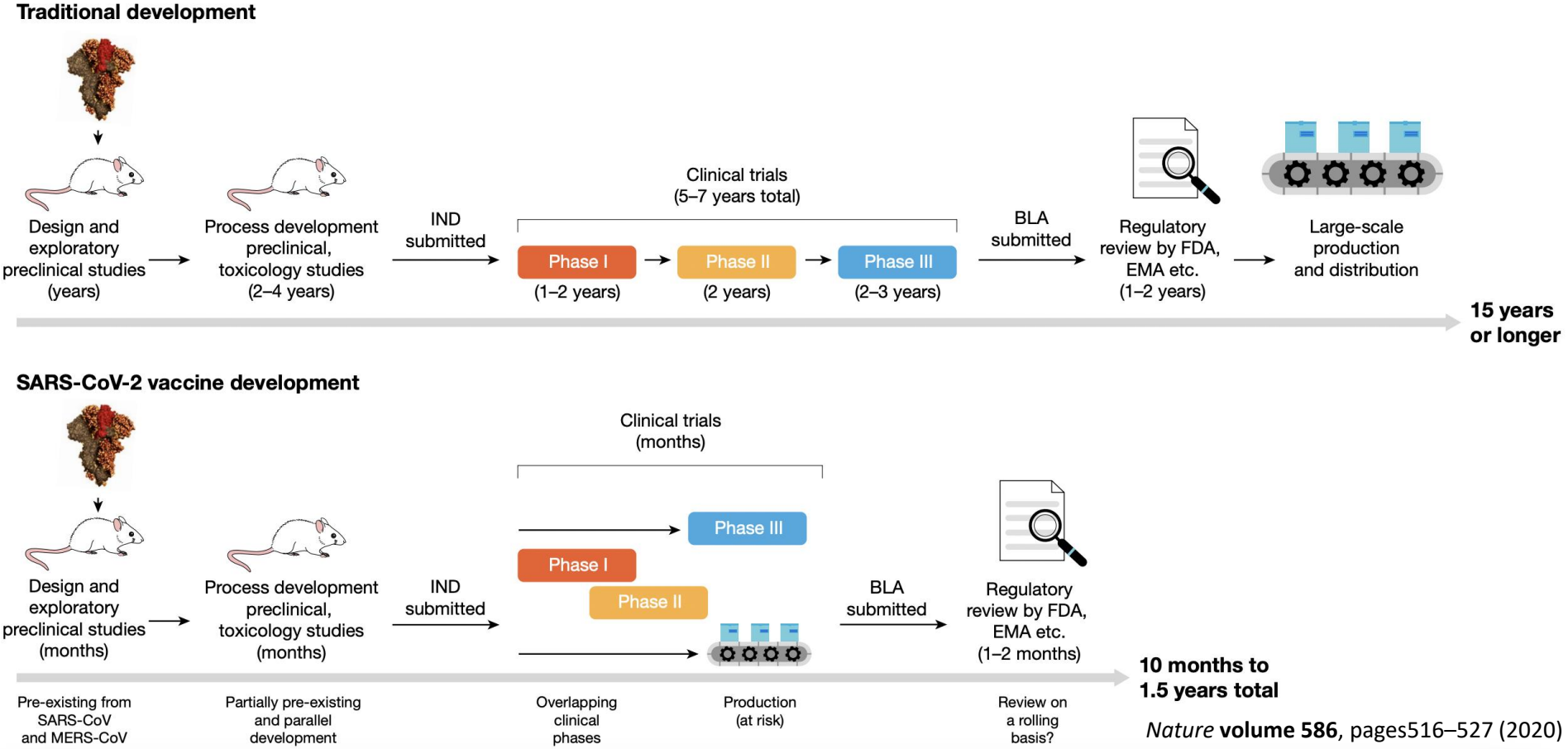
Thrombosis with thrombocytopenia syndrome in COVID-19 vaccines





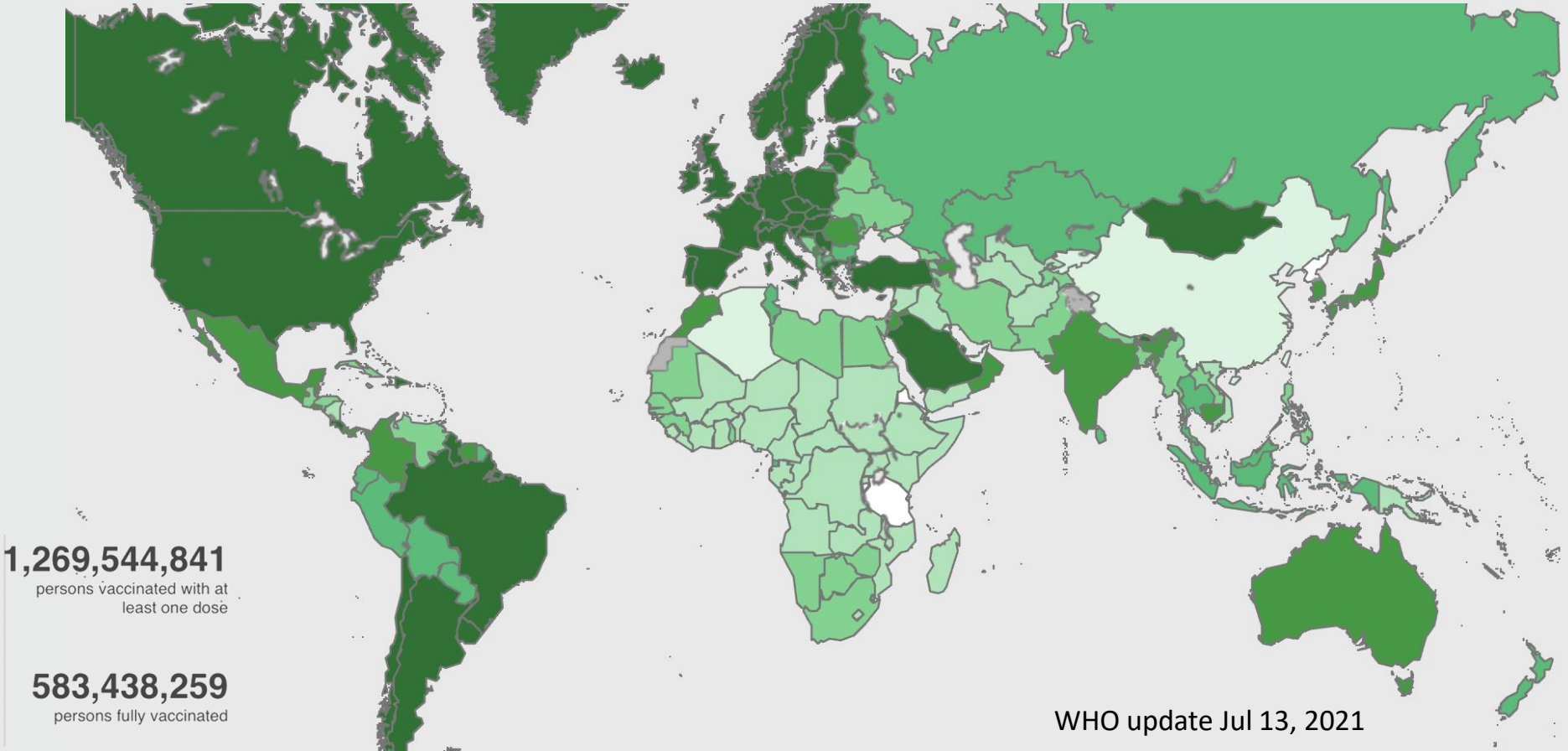
台大醫院血液科
周聖傑醫師

Accelerated vaccine development



Nature **volume 586**, pages516–527 (2020)

COVID-19 vaccine map



WHO update Jul 13, 2021

COVID-19 vaccines

	Mechanism	Shots needed	Protection rate
Astra Zeneca	Adenovirus vector	2	76%
J&J	Adenovirus vector	1	72%
Pfizer/ BNT	mRNA	2	95%
Moderna	mRNA	2	95%
Novavax	Viral protein	2	90%
Sputnik V	Adenovirus vector	2	91%

感謝林氏璧醫師協助提供

TTS: A rare but fatal condition

- 49-year-old, nurse
- AZ COVID-19 vaccination in the middle of February, 2021
- High fever, nausea, epigastralgia since 5th day
- Hospitalized on 10th day
  - Thrombocytopenia, low fibrinogen
  - Very high d-dimer
  - Portal vein thrombosis and pulmonary embolism
- Transfusion of platelet & heparin for thrombosis
  →rapid deterioration, massive GI bleeding
- Death on 11th day
  - Cerebral venous sinus thrombosis found by autopsy

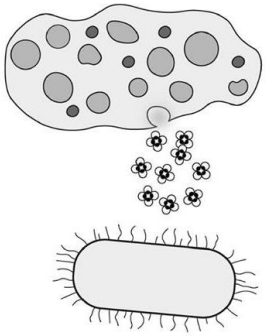
DOI: 10.1056/NEJMoa2104840

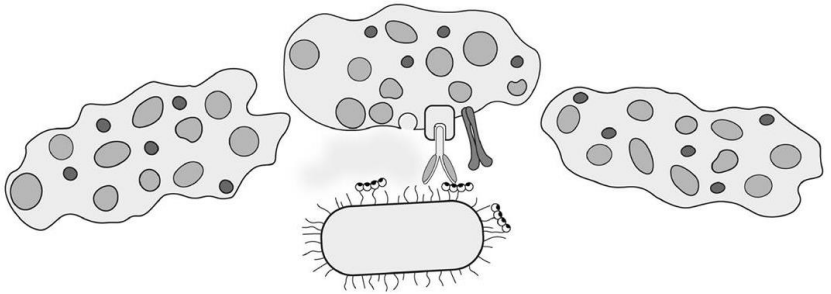
Thrombosis with thrombocytopenia syndrome(TTS)
Vaccine Induced immune Thrombotic Thrombocytopenia (VITT)

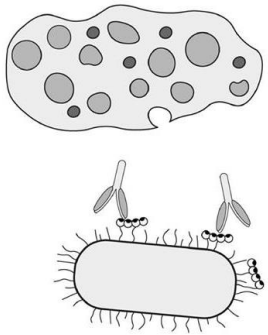
- Mostly found after adenovirus vector-based vaccine (AZ & JJ)
- Incidence: varied with population (around 10 per 1 million)
- Mostly happened on 5-20 days after vaccination
- Unusual site thrombosis: cerebral venous sinus thrombosis, splanchnic venous thrombosis, etc.
- Thrombocytopenia
- Strong anti-platelet factor 4/heparin antibody

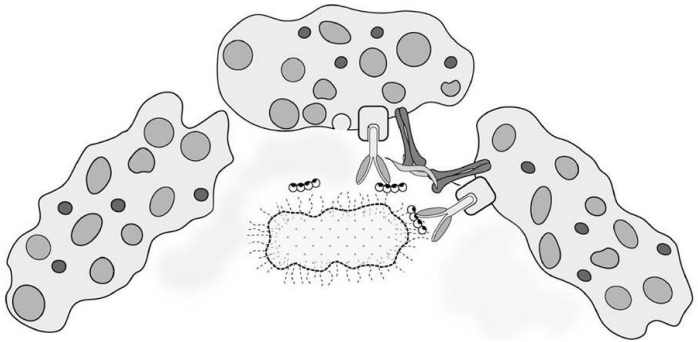
https://doi.org/10.1111/jth.15341

Platelet immunity & Heparin induced thrombocytopenia



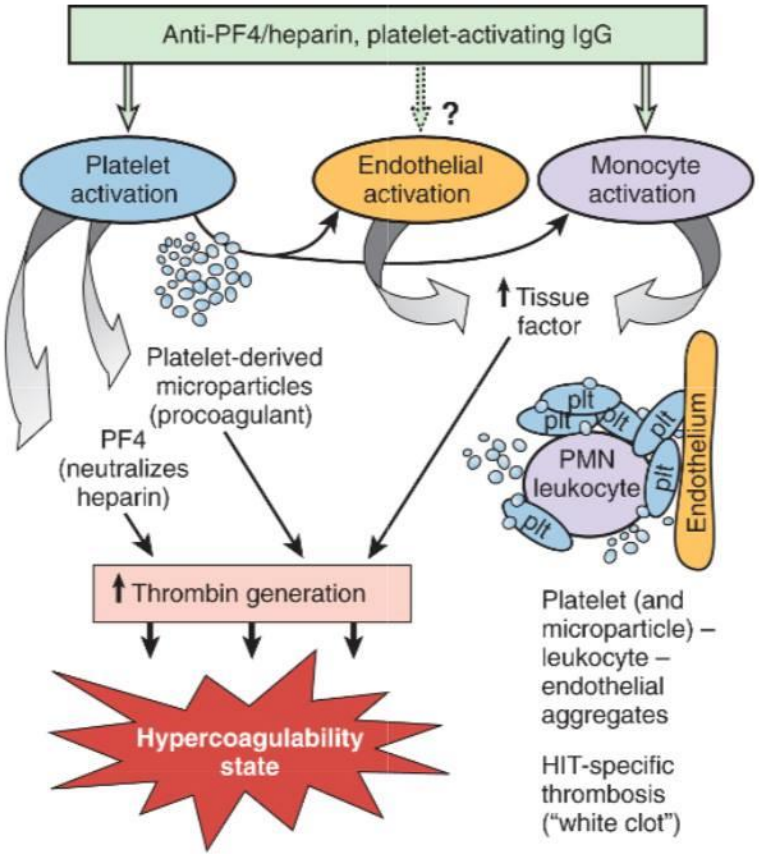






https://doi.org/10.1111/jth.140

Heparin induced thrombocytopenia



https://doi.org/10.1111/jth.14012

VITT/TTS reported incidence

First author/source	Date of publication	Study period	Country	Vaccine	Dose	Cumulative incidence (95% CI) [cases per 100 000 vaccinees]
Schultz (10)	9/4/21	Unknown-20/03/2021	Norway	ChAdOx-1	First	3.8 (95% CI 1.4-9.3)
Spanish Medicines Agency (41)	11/5/21	01/02/2021-25/04/2021	Spain	ChAdOx-1	First	0.5 [1.3 in patients aged 30-39]
Centers for Disease Control and Prevention (39)	12/5/21	Unknown-07/05/2021	United States of America	BNT162b2, Ad26.COV2S	First	Global: 0.32 [1.2 in female patients aged 30-39]
Schulz (18)	13/5/21	Unknown-14/04/2021	Germany	ChAdOx-1 and BNT162b2	First	6.5 (95% CI 4.4-9.2) overall; 17.9 (95% CI 11.8-26.1) for ChAdOx1
Medicines & Healthcare products Regulatory Agency (48)	27/5/21	09/12/2020-26/05/2021	United Kingdom	ChAdOx-1	First and second	1.4 first dose, 0.13 second dose
Chan (43)	Preprint	Unknown-15/04/2021	Norway, Denmark, The Netherlands, Italy, Canada, United Kingdom, Germany, Australia, France, Spain	ChAdOx-1	First	0.73 (95% CI 0.43-1.23). Age <65 years: 1.60 (95% CI 0.71-3.62), Age 55-64 years: 0.41 (95% CI 0.1-1.65)

WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

VITT/TTS risk factors

- Adenovirus vector-based COVID-19 vaccine
- ChAdOx1-s (AZ) > Ad26.COV2-S (J&J)
- Middle or young age

- **Pre-existing thrombosis risk factors is NOT related to either incidence or severity**

WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

VITT symptoms and signs

- Symptoms and signs of thrombosis
  - Severe and persistent headache/ vision changes/ seizure
  - Severe and persistent abdominal pain (> 24 hr)
  - Pain and swelling of legs
  - Chest pain and/or shortness of breath
- Timing: within 30 days after COVID vaccination
- Combination of thrombosis and thrombocytopenia
- Screening test: platelet count, d-dimer, fibrinogen

WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

https://cdn.ymaws.com/www.isth.org/resource/resmgr/ISTH_VITT_Guidance_2.pdf

VITT/TTS diagnostic criteria-1

Classification	Major criteria	Minor criteria
Thrombosis	**CONFIRMED** diagnosis of thrombosis by imaging study, surgical, or pathology findings consistent with thrombosis/thromboembolism in an **uncommon location**: • cerebral veins OR • splanchnic veins OR • multiple organ	**CONFIRMED** diagnosis of thrombosis by imaging study, surgical, or pathology consistent with thrombosis/thromboembolism in a **common location:** • pulmonary arteries/veins OR • limb veins OR • coronary arteries OR • cerebral arteries OR • other arteries/veins OR **SUGGESTIVE** thrombosis by supporting imaging or

WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

VITT/TTS diagnostic criteria-2

Classification	Major criteria	Minor criteria
Thrombocytopenia	Platelet count: <50 x 10^9/L AND Confirmatory peripheral smear showing reduced platelets AND No evidence of platelet clumping	Platelet count: > 50 x 10^9/L - <150 x 10^9/L OR >50% decrease from baseline platelet count
Laboratory (other than thrombocytopenia)	Positive anti-platelet factor 4 antibodies (with ELISA) or platelet functional assay (i.e., serotonin release assay)	D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)

WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

VITT/TTS diagnosis

Classification	Level 1 (Confirmed case)		Level 2 (Probable case)		Level 3 (Possible case)
Thrombosis	Major / Minor	Major	Minor	Major	Minor
Thrombocytopenia	Major / Minor	Major	Major	Minor	Minor
Laboratory (Other than thrombocytopenia)	Major	Minor	Minor	Minor	Minor / No laboratory

WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

Simplified algorithm-1

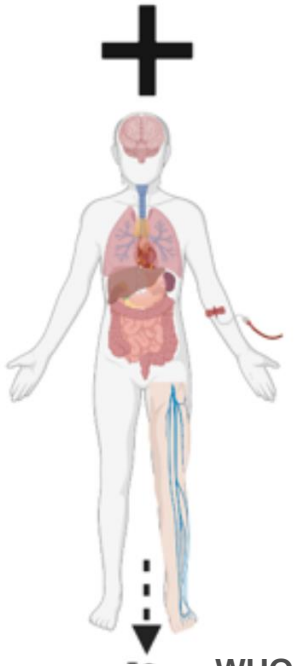
Thrombosis

Uncommon location

Cerebral venous sinus thrombosis
Splanchnic thrombosis
Multiple organs

Common location

Ischemic stroke
Pulmonary embolism
Myocardial infarction
Deep vein thrombosis

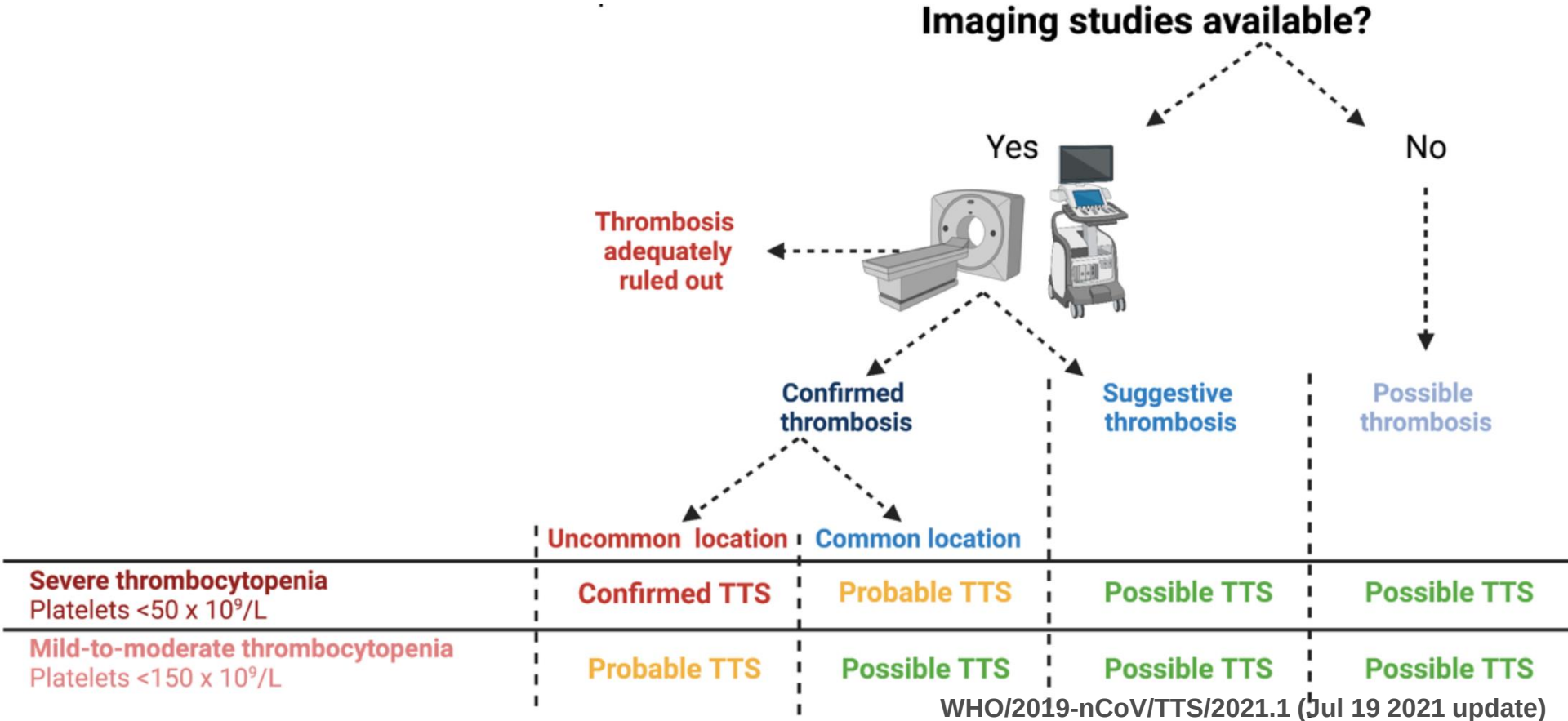


Thrombocytopenia

Platelets <150 x 10^9/L
Platelets <50% baseline

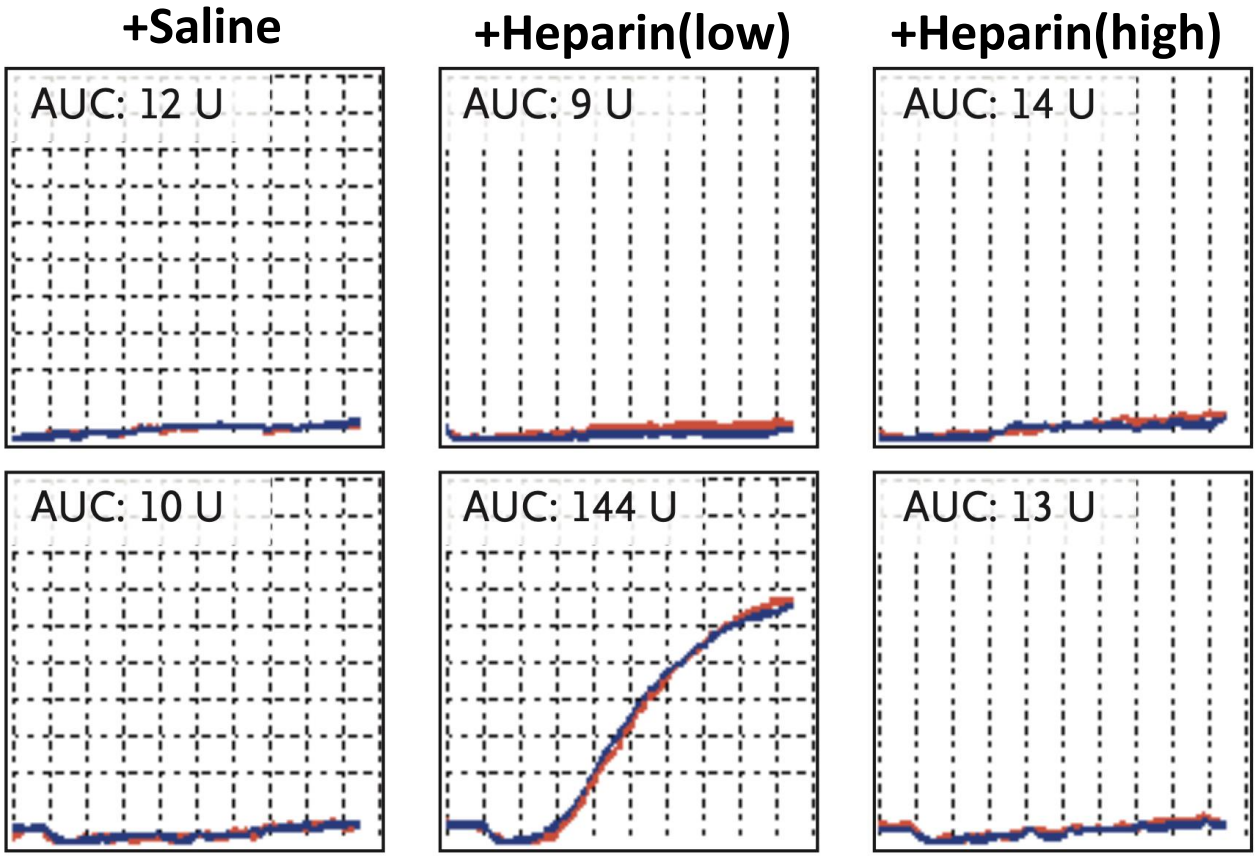
WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

Simplified algorithm-2



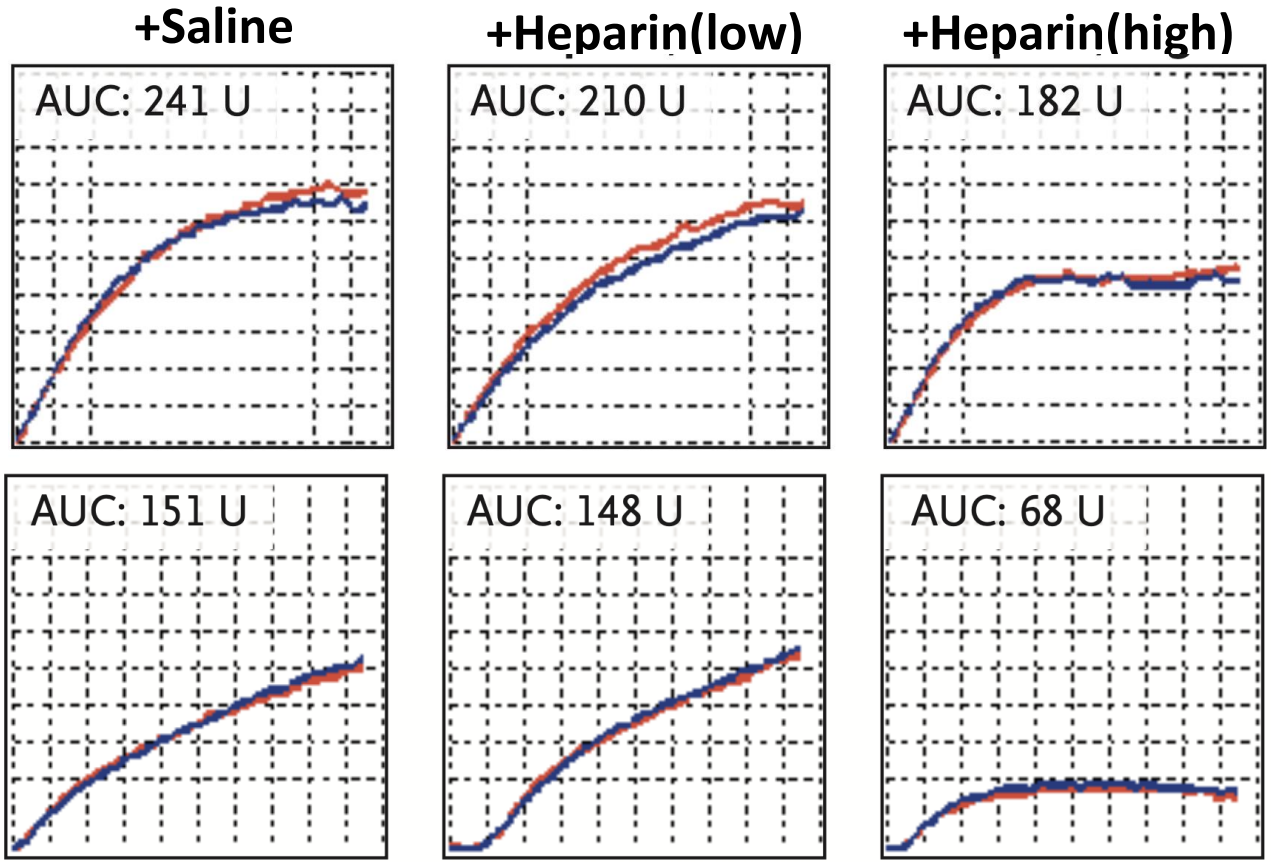
WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

Functional platelet activation assay (control)



DOI: 10.1056/NEJMoa2104882

Functional platelet activation assay (VITT)

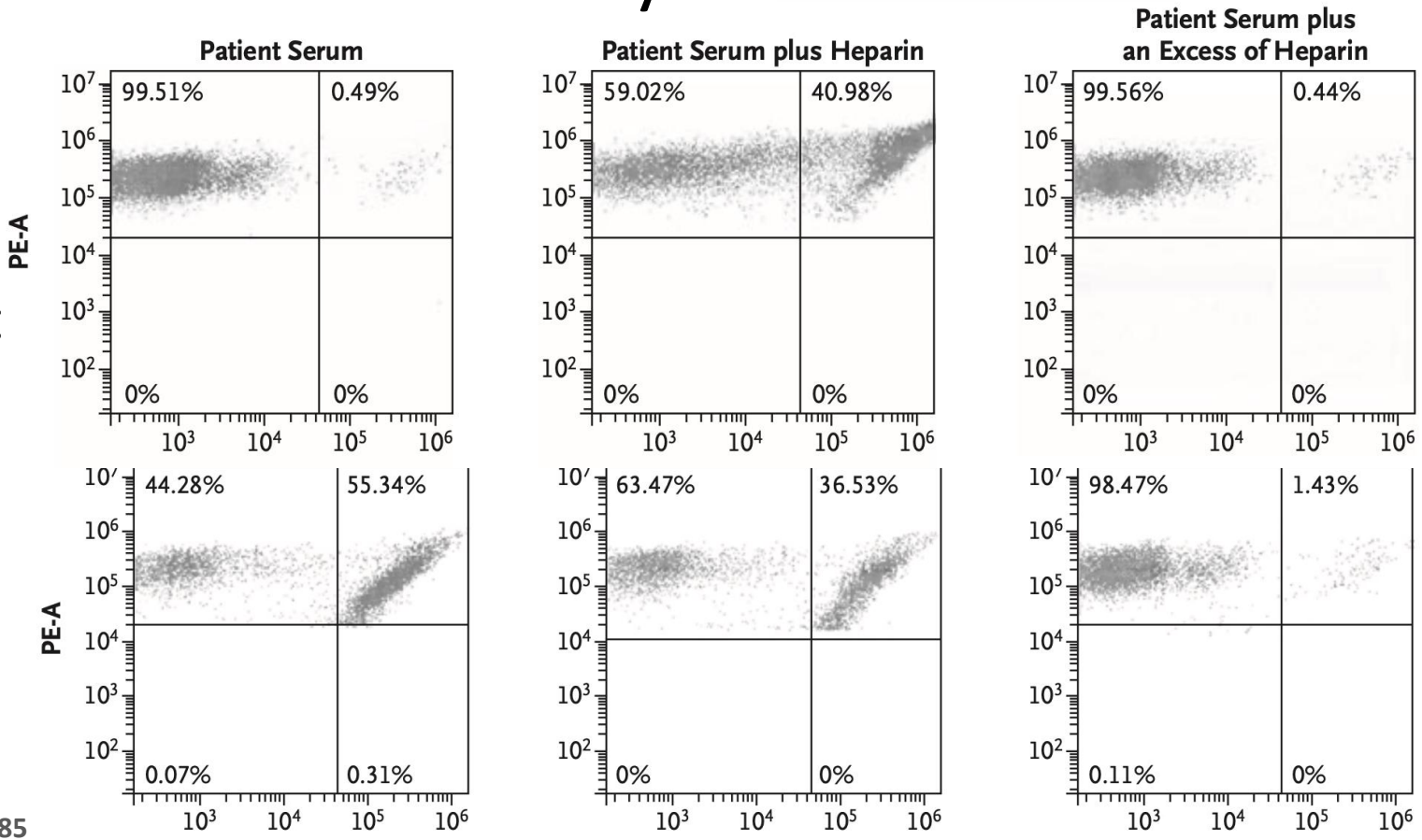


DOI: 10.1056/NEJMoa2104882

Functional assay flow-based

HIT
+donor plt

VITT
+donor plt



10.1056/NEJMoa2105385

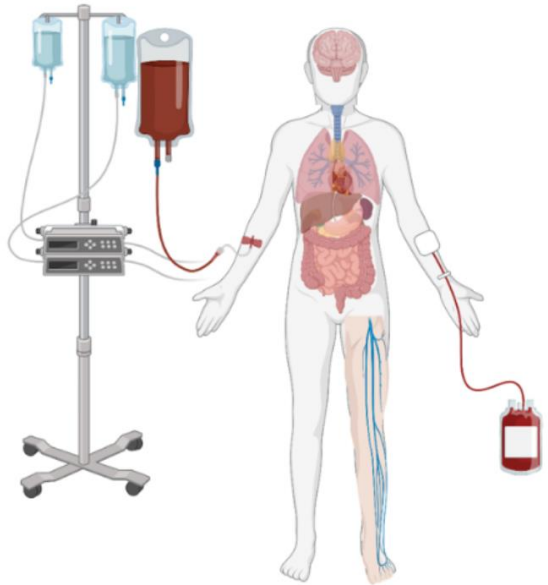
VITT management

Avoid platelet transfusions
In all cases other than emergency situations where surgery is strongly indicated, thrombocytopenia is severe, and platelet transfusion is required to be able to proceed with emergency surgery

Avoid heparin based anticoagulation
For individuals with TTS following vaccination with a COVID-19 vaccine

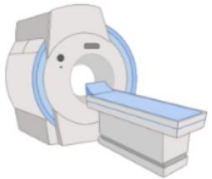
Administer non-heparin based anticoagulants
Argatroban, bivalirudine, fondaparinux, danaparoid, rivaroxaban, apixaban, dabigatran

Consider IV Immunoglobulins
1 g/kg x 2 days or 0.4g/kg x 5 days



PCR test for COVID-19

Monitor platelet count

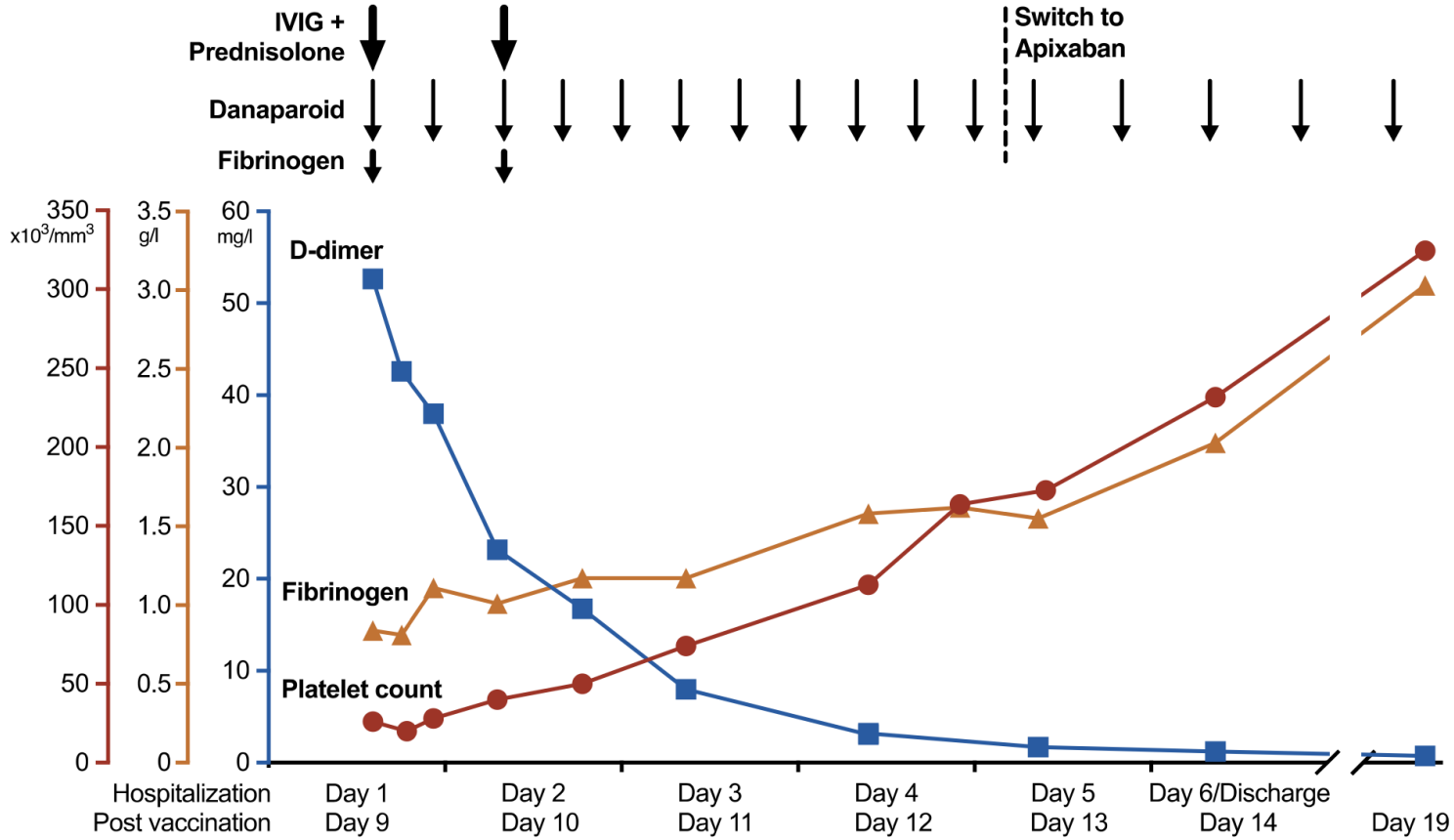


Complete examinations per patient

Report the case

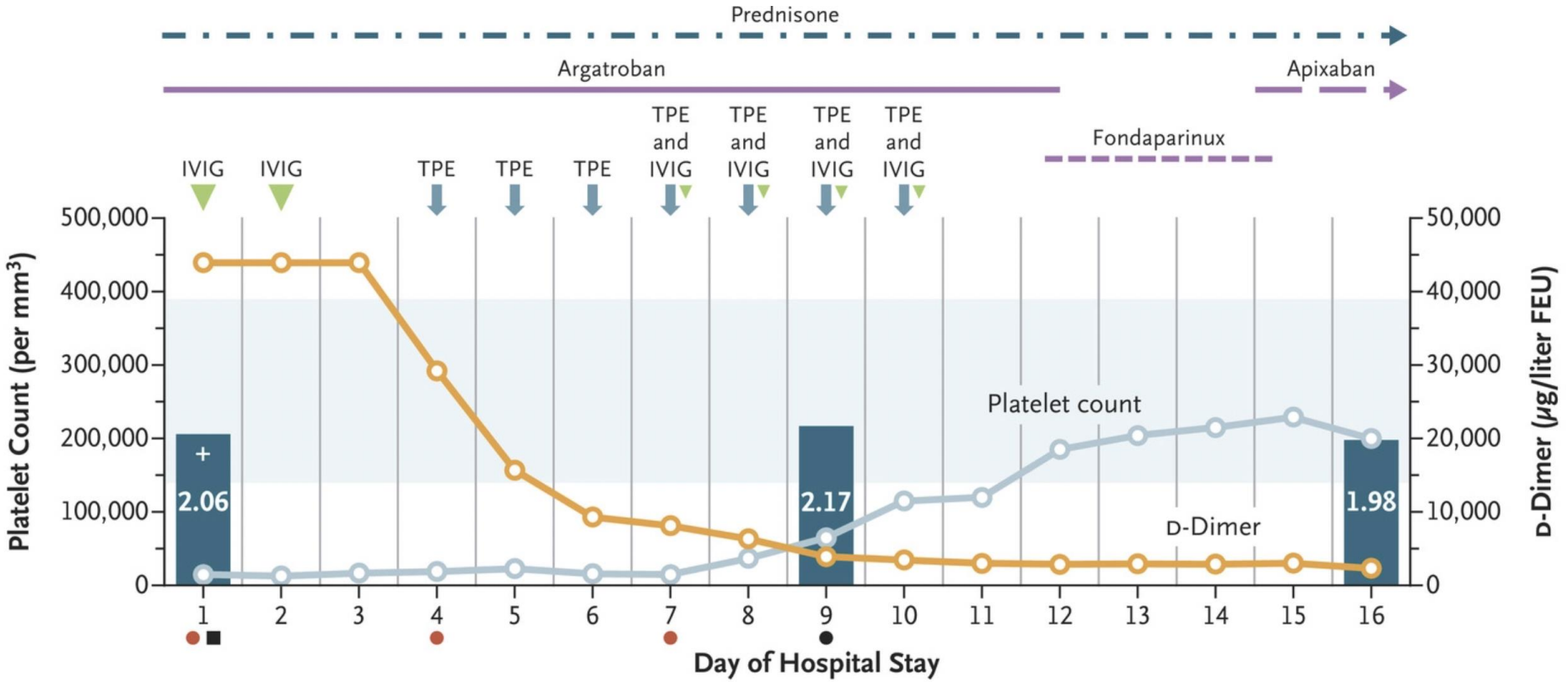
WHO/2019-nCoV/TTS/2021.1 (Jul 19 2021 update)

Successful VITT case with IVIG + steroid



doi: 10.1111/JTH.15346

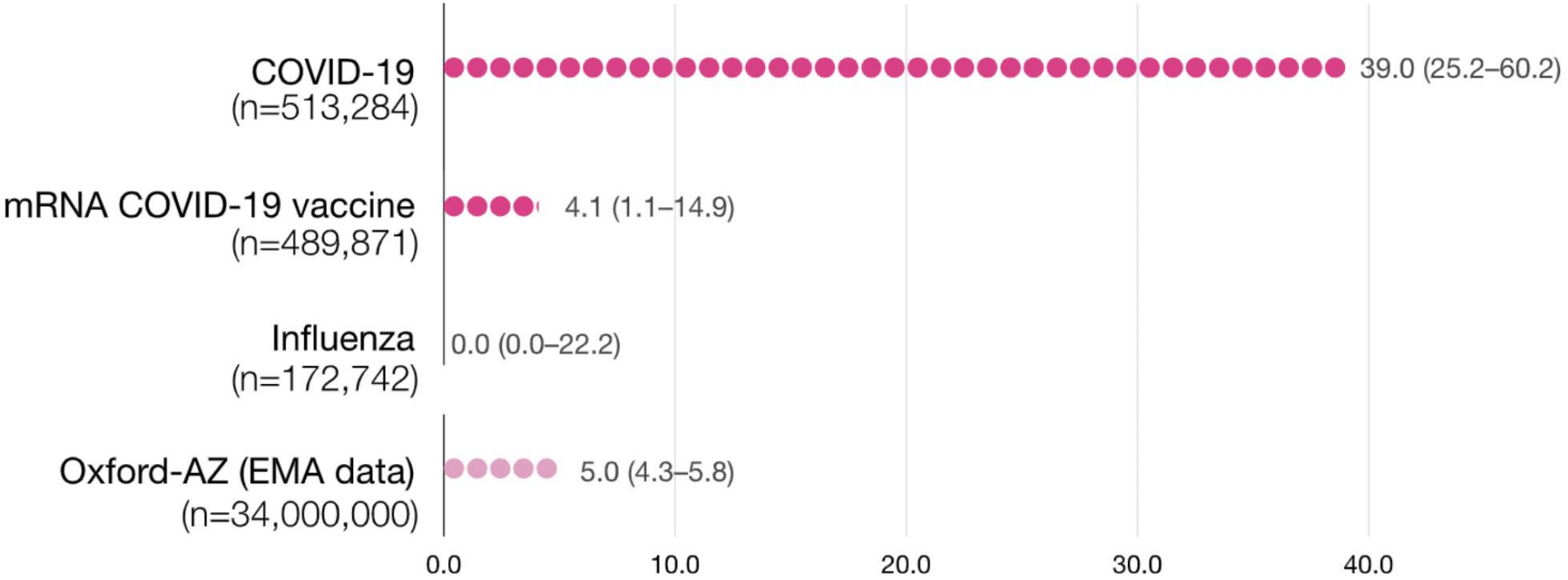
Successful VITT case-2 with TPE



DOI: 10.1056/NEJMc2109465

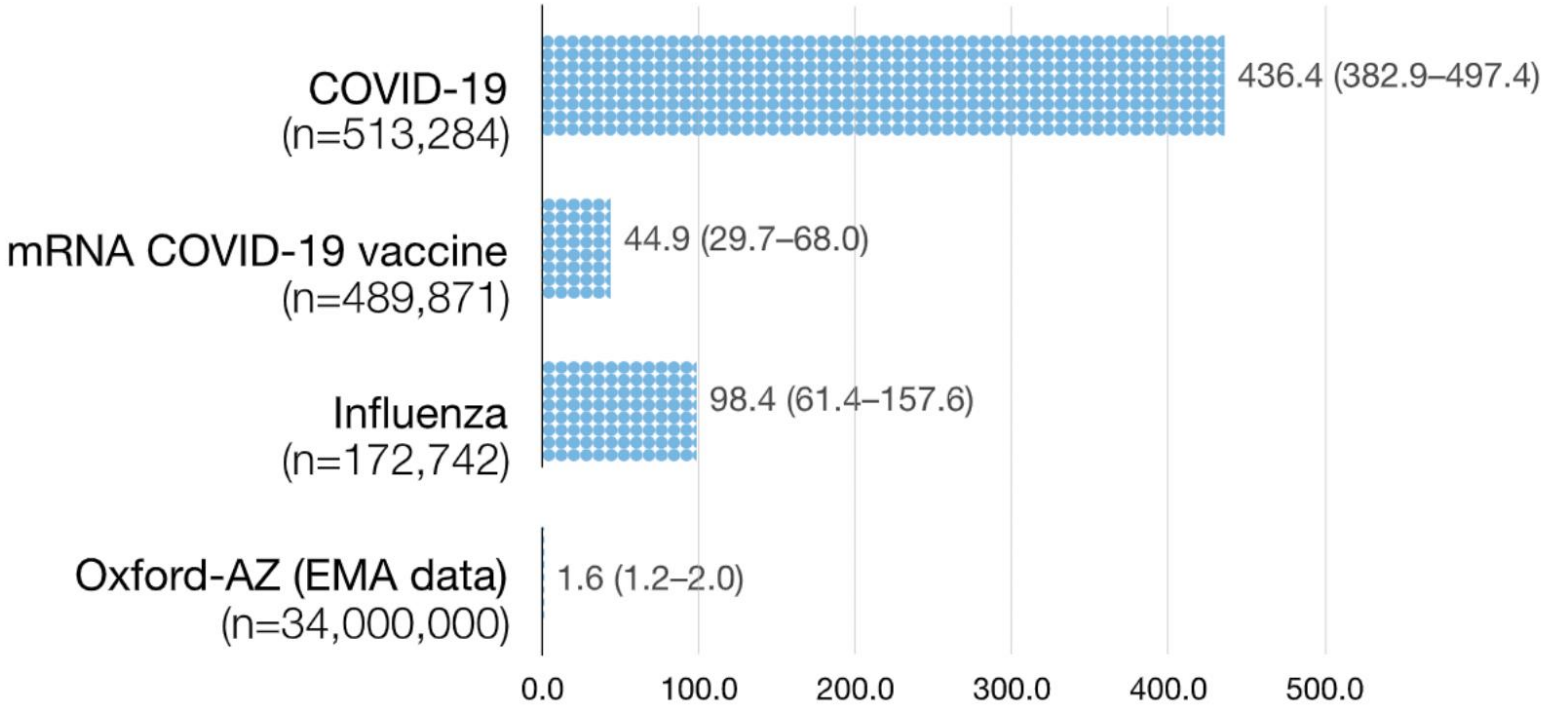
COVID-19 vaccine vs. COVID-19

CVST（ per 1,000,000 person/ 2 weeks ）



COVID-19 vaccine vs. COVID-19

Portal vein thrombosis（ per 1,000,000 person/ 2 weeks ）



COVID-19 vaccine associated VITT/TTS summary

- Thrombosis + thrombocytopenia
- Mechanism is similar to HIT
- Incidence: rare, around 10 per million
- Risk factor: adenovirus vector-based vaccine, age
  Pre-existing thrombosis risk factor is not related
- High d-dimer, low fibrinogen and strong anti-PF4
- Avoid platelet transfusion/heparin/LMWH
- Treatment: IVIG, steroid, non-heparin anticoagulant, TPE