Diagnosis and management of Thrombosis and thrombocytopenia Syndrome or Vaccine induced Thrombosis and Thrombocytopenia (TTS/VITT)

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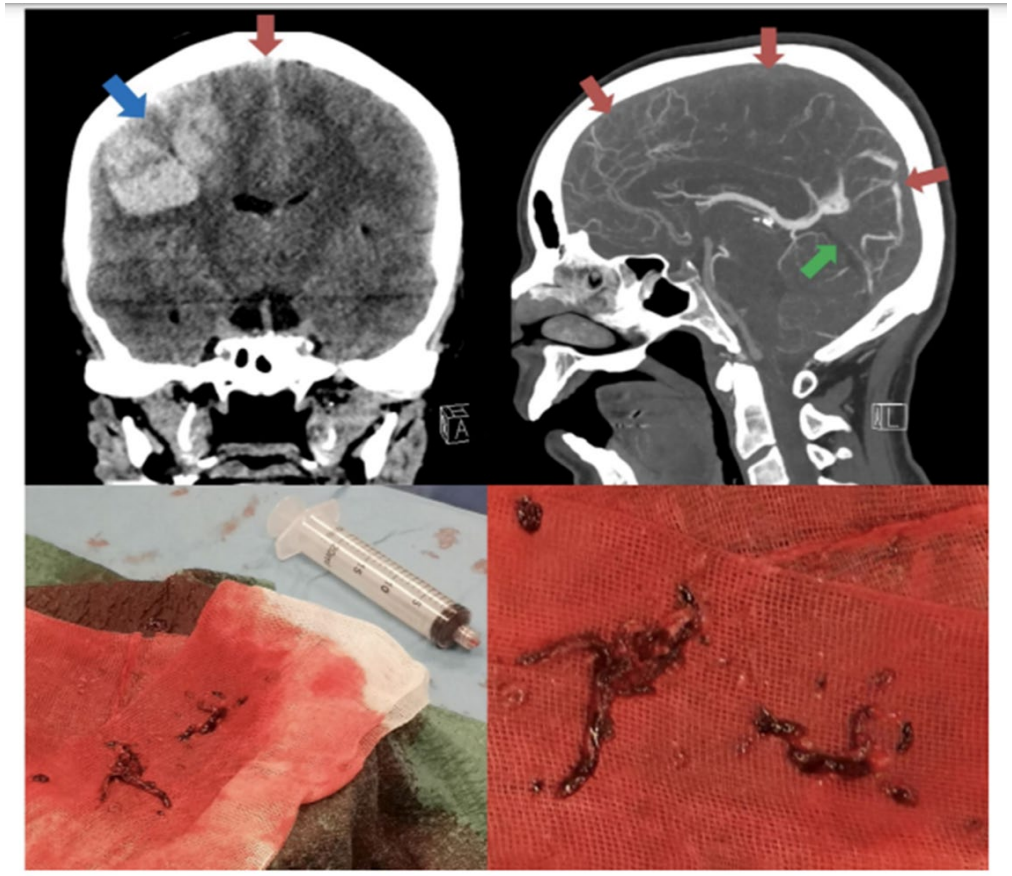
THANZ VITT Advisory Group.



Objectives

- Perspective of serious thrombotic complications of AZ vaccine (ChadOx1)
- Understand the diagnostic algorithm for TTS
- Early recognition of TTS
- Example of Management of TTS
- Approach to previous thrombosis/ thrombocytopaenia and vaccination

Panel discussion Q & A and Conclusion

Perspective and context : Australian data

Total adverse event reports to 27 June 2021

4.6	33,807	7,374,666
Reporting rate per 1000 doses	Total AEFI reports received	Total doses administered
23,235	10,314	263
Total reports for AZ vaccine	Total reports for Comirnaty	Total reports for brand not specified

Reporting rates per 1000 doses by jurisdiction

Australian Capital Territory	4.0	New South Wales	3.4

Source TGA 01 July 2021

Age	Total cases	CDC classification†		
		Tier 1	Tier 2	Not classified
<30 years				
30-39				
40-49				
50-59				
60-69				
70-79				
80+				
All ages	**69** **(34 men, 35 women)**	26	20	23

Table 3: Time to onset, treatment and outcomes for TTS cases*

Time to onset/ diagnosis (days)	Median (range)	12 (1-44)
Treated in ICU	At any point†	18
	Currently	3
Outcome	Discharged	51
	In hospital	16
	Fatal	2

Source TGA 06 July 2021

Diagnostic criteria for TTS

† The US CDC classification is defined as:

- Tier 1 = clots in an unusual location (such as the brain or abdomen) **and** a low platelet count with or without antibodies that activate platelets (anti-PF4 antibodies)
- Tier 2 = clots found in common locations (such as the leg or lungs) and a low platelet count **and** anti-PF4 antibodies
- Not classified = case does not meet the criteria for Tier 1 or Tier 2 (for example clots in common locations with **low** platelet count but no evidence of anti-PF4 antibodies).

Abbreviation	Stands for	Comments
VIPIT	Vaccine Induced Prothrombotic Immune Thrombocytopenia	Original term reported by German researchers.
VITT	Vaccine Induced immune Thrombotic Thrombocytopenia or Vaccine Induced immune	Term used in subsequent report by the German group, as well as separate case series by Norwegian, UK and French based groups publishing in NEJM. Probably reflecting a

Abbreviation	Stands for	Comments
TTS	Thrombosis with Thrombocytopenia Syndrome	A term favoured by some reporting agencies that does not specifically reference any 'vaccine' association. Term not typically utilised by researchers for the condition associated with COVID-19 vaccine use, since essentially can encompass any condition where thrombosis can be associated with thrombocytopenia, including HITT, severe or catastrophic antiphospholipid (antibody) syndrome (APS or CAPS) and thrombotic thrombocytopenia purpura (TTP).

POLL 1. The CDC TTS case definition tier 1 requires

- Thrombosis at an unusual site and thrombocytopenia
- Thrombosis at a usual site, thrombocytopenia and positive PF4 antibody
- Thrombosis at a usual site, thrombocytopenia and positive
- functional platelet activation test

CDC CASE definitions

- Tier 1 TTS case
  - Thrombosis in an unusual location, including cerebral venous sinuses, portal vein, splenic vein, and other rare venous and arterial thromboses
    - May also concurrently have thrombosis in more common locations (e.g., venous thromboembolism, axillary vein thrombosis, deep vein thrombosis, pulmonary embolism)
  - Platelet count <150,000 per microliter
  - Positive (+) heparin-PF4 ELISA HIT antibody* result is supportive, but not required
- Tier 2 TTS case
  - Thrombosis in a common location only (e.g., venous thromboembolism, axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, etc.)
    - Excludes isolated acute myocardial infarction or ischemic stroke
  - Platelet count <150,000 per microliter
  - Positive (+) heparin-PF4 ELISA HIT antibody* result is required

Case 1

52-year-old female
Headache , nausea, vomiting
No lower limb swelling
12 days post AZ vaccine
ECOG 0, very active
OCP related below knee DVT in her twenties
SLE (non –active) and not on any treatment

CASE 1 day 7 post AZ vaccine (5 days prior)

Wd Emergency (JHH) Doc Dr Dragan Petkovi* Sp Blood CollT 11:11 26-Apr-21

Full Blood Count Report Status - FINAL Specimen Received Time - 11:58

WBC	4.5	NEUT	74	%	3.3			
RBC	4.28	BAND		%		OTHER		%
HGB	132	LYMPH	22	%	1.0	NRC		/100 WBC
HCT	0.392	MONO	3	%	0.1 L	ANRC	0.0	/100 WBC
MCV	92	EOSIN	0	%	0.0			
MCH	31	BASO	1	%	0.0			
MCHC	337	MET		%		WBC	4.5	
RDW	13.6	MYE		%		UNWBC	4.5	
PLT	151	PRO		%				
MPV	9.2	BLA		%				

Lower limb pain
USG lower limb normal

HAEMATOLOGY - COAGULATION TESTING Specimen: Blood

		Range	Units
PT	14	(11 - 16)	s
INR	0.9		
APTT	28	(24 - 36)	s
Fibrinogen	4.5 H	(2.0 - 4.0)	g/L
D-dimer	11 C	(< 0.50)	mg/L
D-Dimer Interpretation	POSITIVE (refer to comment)		

CASE 1 RETURNS

D/C Home from ED as pain had resolved

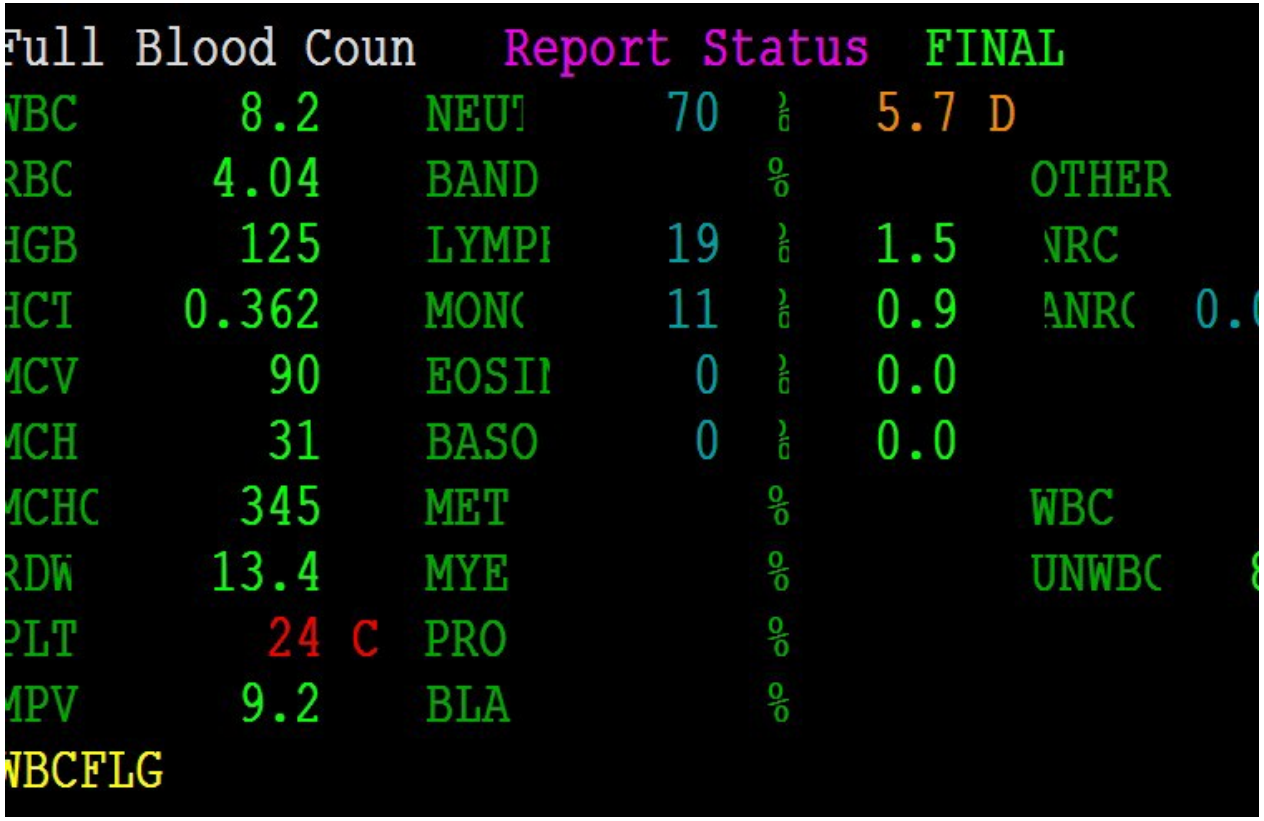
On day 11 post AZ developed worsening generalised headache, malaise, and rigours

Day 12, headache persisted and progressed to intractable vomiting. Presented to Private ED and subsequently transferred to JHH ED

No focal neurology at that time on examination

No other symptoms to suggest other sites of pathology

CASE 1 RETURNS



Full Blood Coun		Report Status	FINAL		
WBC	8.2	NEUT	70 %	5.7 D	
RBC	4.04	BAND	%		OTHER
HGB	125	LYMPH	19 %	1.5	NRC
HCT	0.362	MONO	11 %	0.9	ANRC 0.(
MCV	90	EOSIN	0 %	0.0	
MCH	31	BASO	0 %	0.0	
MCHC	345	MET	%		WBC
RDW	13.4	MYE	%		UNWBC 8
PLT	24 C	PRO	%		
MPV	9.2	BLA	%		
WBCFLG					

		Range	Units
PT	19 D	(11 - 16)	s
INR	1.3 D		
APTT	38 H	(24 - 36)	s
Fibrinogen	0.6 C	(2.0 - 4.0)	g/L
D-dimer	>20 C	(< 0.50)	mg/L
D-Dimer Interpretation	POSITIVE (refer to comment)		

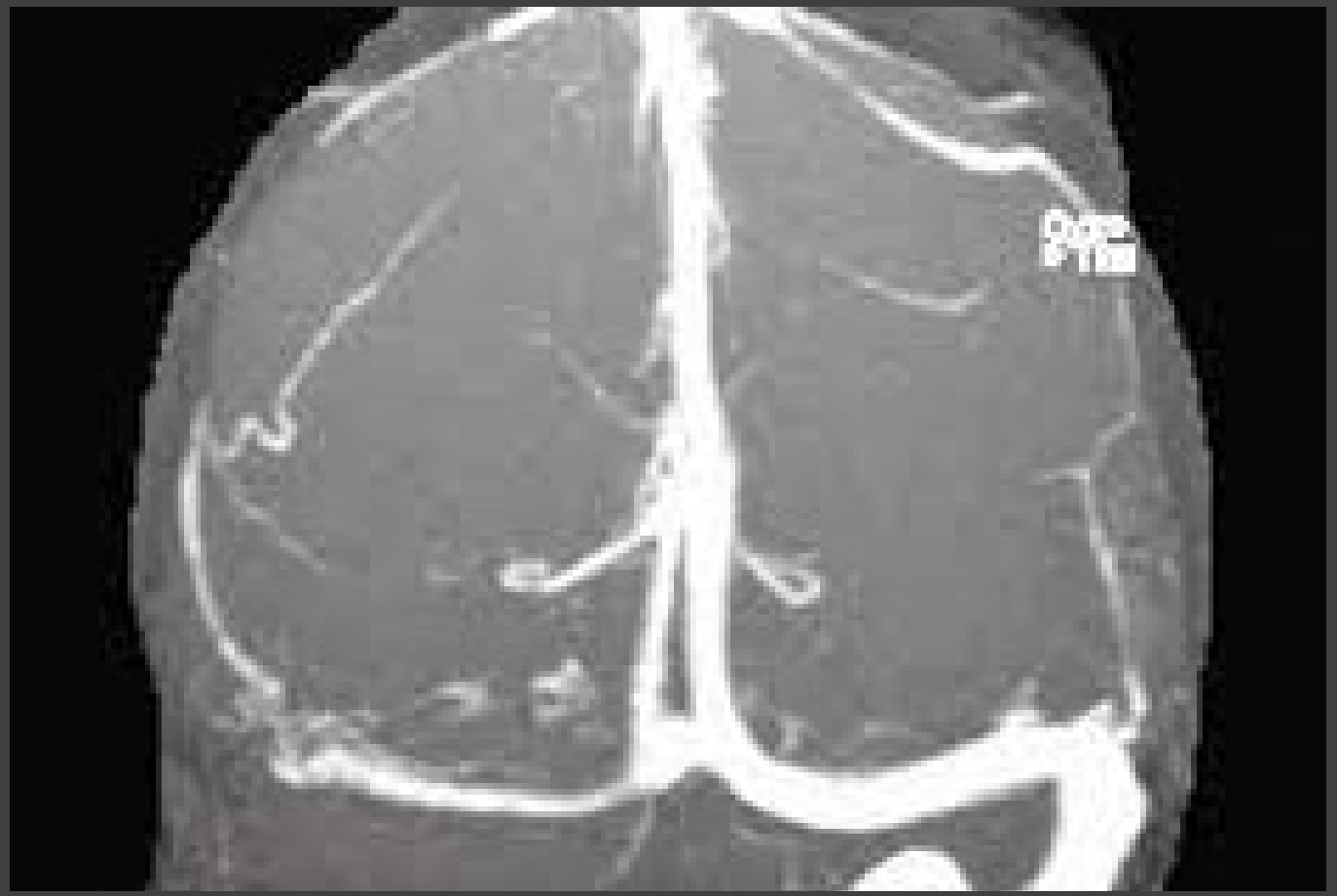
CASE 1 RETURNS

HAEMATOLOGY - LUPUS ANTICOAGULANT TESTING.

APTTLS	47.9	(25.0 - 53.0)
DRVLS	50.4	(29.0 - 51.0)

Lupus Anticoagulant :
No evidence of a Lupus Inhibitor.

Cardiolipin IgG-CIA	12
Cardiolipin IgG	Negative
Anti-B2GP1	< 6



CT Venogram

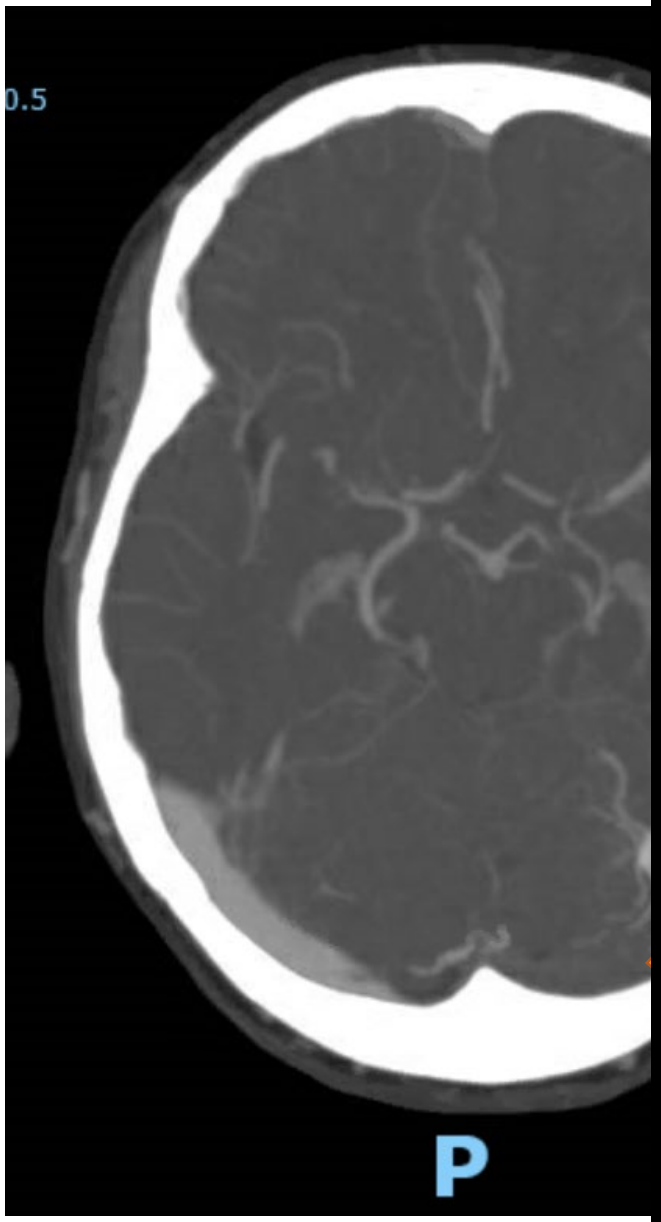
CASE 1 RETURNS - PROGRESS AND MANAGEMENT

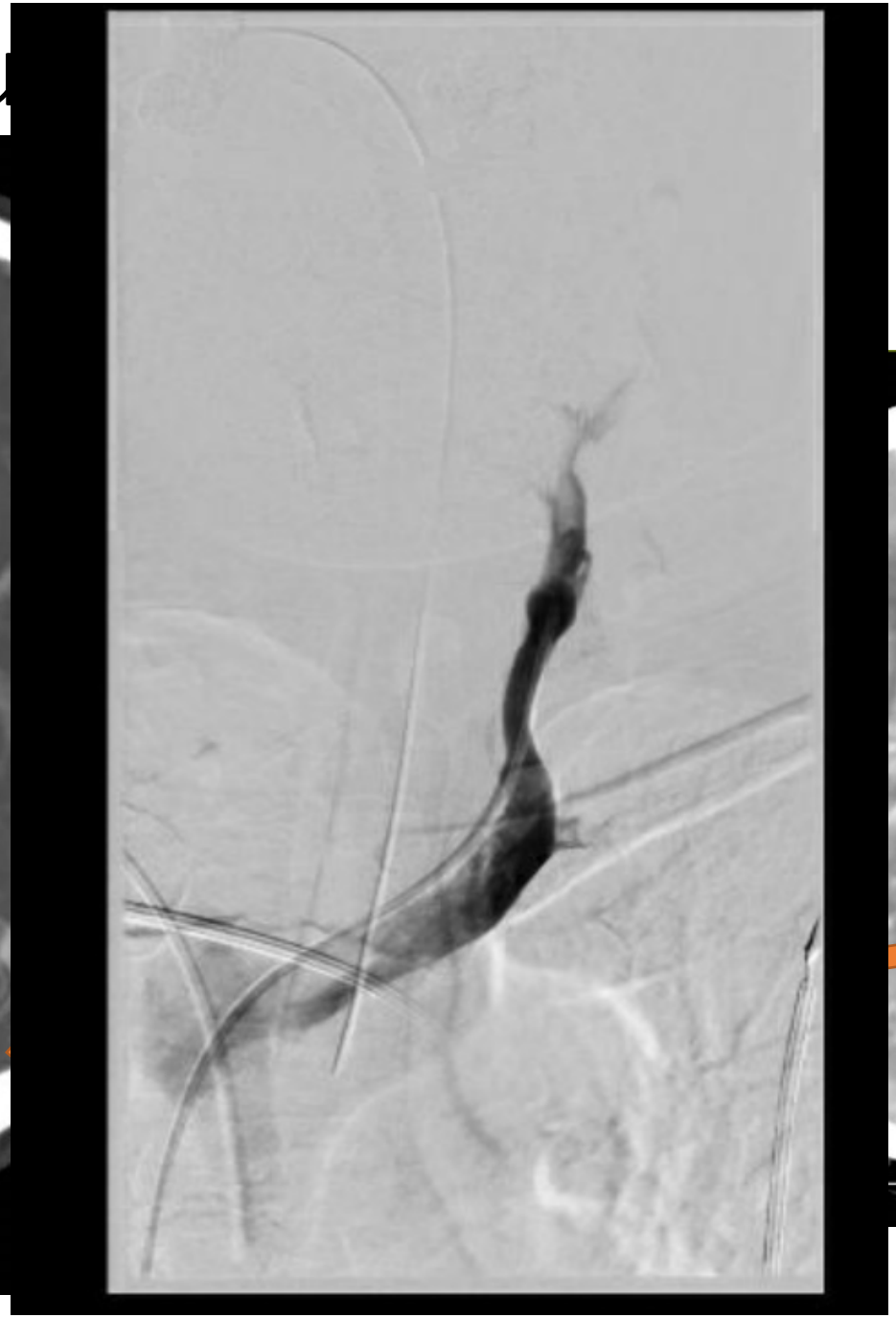
Initial VITT treatment:

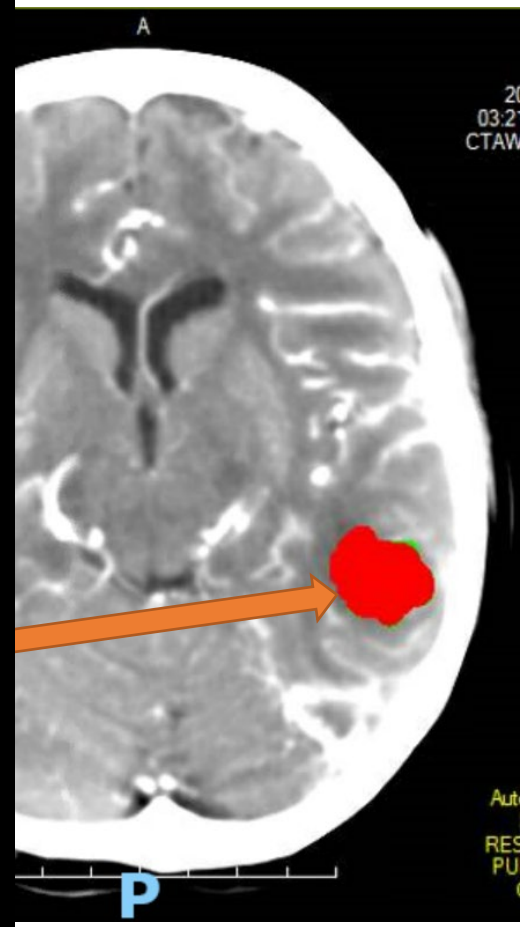
- Given 4 units of Cryoprecipitate due to low Fibrinogen
- Given IVIG 2G/KG over 2 doses
- Commenced on Argatroban infusion
- Monitored using aPTT

Day 2 of admission, developed new expressive dysphasia and ataxia

The next 24 hou







VITT Testing

- AcuStar heparin:PF4 Ab - not detected
- Further testing
  - HITS/VITT ELISA - positive
  - Functional SRA - positive
  - Flow cytometry - positive
  - Multiplate - positive

CASE RETURNS - PROGRESS

Initial VITT treatment:

- Given 4 units of Cryoprecipitate due to low Fibrinogen
- Given IVIG 2G/KG over 2 doses
- Commenced on Argatroban infusion

Day 2 of admission, developed new expressive dysphasia and ataxia

- Repeat urgent CT Brain: New left temporal haemorrhage
- In discussion with Interventional neurologist, proceeded to

thrombectomy of left cerebral venous sinus (D2), and admitted to ICU

for ongoing monitoring and argatroban infusion titration

Management and recovery

Platelets recovered to 164 on day 4 of admission (day 16 post AZ)

Neurology stabilized and over the next several days began to improve

Continued on Argatroban for 4 days post clot retrieval until

neurology began to improve and haemorrhage appearance stable on

repeat imaging

- Transitioned to Dabigatran
- Discharged to Stroke Rehab and progressing well

Management principles of suspected TTS/VITT

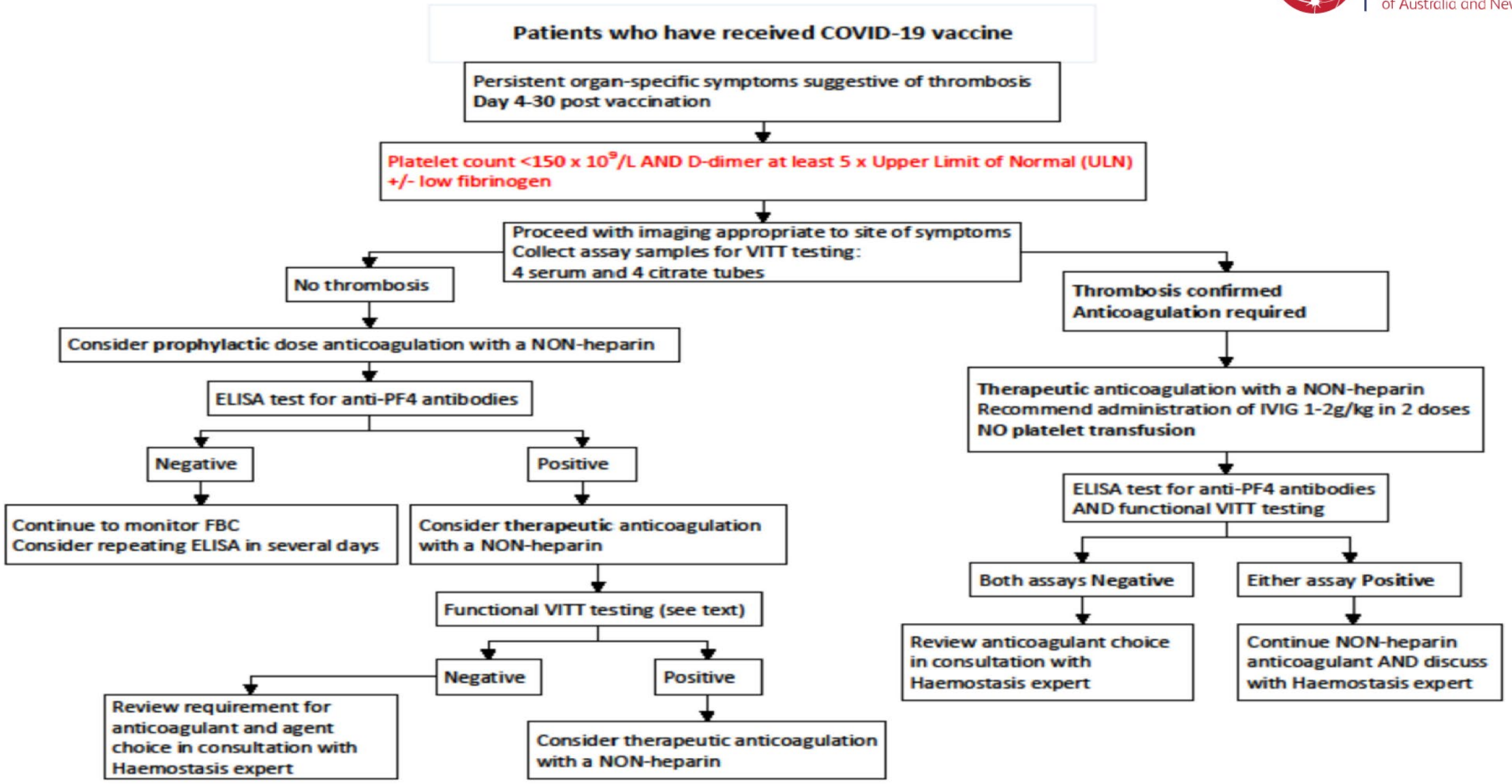
- Testing for presence of anti-PF4 antibodies (**selected reference labs only**)
- Use non-heparin anticoagulants (e.g. IV Argatroban, IV bivalrudin, IV danaparoid, SC fondaparinux, or direct oral anticoagulants)
- Avoid platelet transfusions, except if bleeding or for neurosurgical interventions
- Consider IV immunoglobulin (or plasma exchange for very severe cases)

Poll 2.What are the first tier lab tests to do in suspected VITT?

- Platelet count, d-dimer
- Platelet count, d-dimer and Fibrinogen
- Platelet count and fibrinogen
- Platelet count, d-dimer and anti-PF4 antibodies

THANZ Advisory Group on VITT

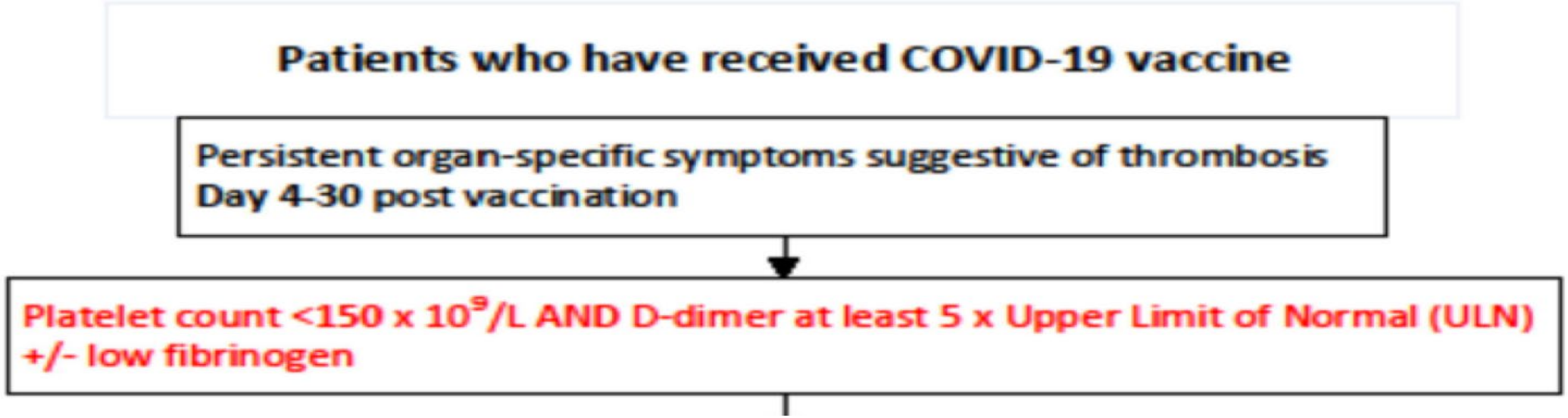
THANZ
Thrombosis & Haemostasis society of Australia and New Zealand



https://www.thanz.org.au/resources/covid-19

First tier lab tests in suspected VITT

- All published cases to date…
- Thrombocytopenia (platelet count <150 x 10^9/L)
- High D-dimer (typically very high, or > 5 x upper limit of normal)
- Most cases (~70%) fibrinogen <2g/L



THANZ Multidisciplinary† VITT Guideline for Doctors

Background

A severe prothrombotic syndrome associated with thrombocytopenia has been described in a small number of patients exposed to the COVID-19 AstraZeneca and Janssen (Johnson & Johnson) vaccine. This syndrome is currently being called several names: VITT (vaccine-induced immune thrombotic thrombocytopenia), TTS (thrombosis with thrombocytopenia syndrome), and VIPIT (vaccine-induced prothrombotic immune thrombocytopenia). For the purposes of this Thrombosis & Haemostasis society of Australia New Zealand (THANZ) Multidisciplinary guideline, the term VITT will be used. It has been observed in early reported cases that platelet transfusions and administration of heparin may lead to progressive thrombosis.

VITT: How to investigate and manage

Patient presents with acute onset symptoms/ signs of thrombosis or thrombocytopenia* AND received AZ or Janssen (JJ) COVID-19 vaccine in last 42 days

DO NOT give heparin anticoagulant
Obtain URGENT FBC, APTT, PT, fibrinogen and D-dimer within 4 hours

Platelets < 150 x 10^9/L **and** D-dimer at least 5 times upper limit of normal (ULN) +/- low fibrinogen†

NO

VITT unlikely
- Consider alternative diagnoses including vaccine-unrelated VTE and investigate and manage accordingly
- GP/outpatient follow up for resolution of symptoms or repeat blood tests and/or imaging if symptoms persist

YES

- High D-Dimer with normal platelet count and thrombosis- repeat platelet count within 1-3 days.
- **tempo of disease can be catastrophic within hours**

  strongly advise careful clinical review of persistent symptoms with repeat screening blood tests in patients with high index of suspicion.

Approach to VITT in the emergency department

Blood test results

	platelet count < 150 x 10^9	platelet cou normal
D-dimer < 5 x ULN	TTS suspected	TTS unli exit pat
D-dimer > 5 x ULN	TTS likely	TTS pos consider sy alternative and repea

ULN = upper limit of normal (not age-adjusted)

If TTS suspected or likely
obtain urgent haematology advice
Treat as per guidance from Expert Haematology Panel
Do not use heparin anticoagulant

Appropriate imaging and other specialty referral as indicated based on clinical presentation
e.g. Cerebral venous sinus thrombosis (CVST) → Neurology

ACEM Guidelines May 2021

Lab testing in suspected VITT triaged according to information received

Australia and New Zealand VITT/VIPIT ELISA and functional testing request form

Suspected Vaccine-induced Thrombotic Thrombocytopenia Blood test request form

*Please complete this form whenever samples from patients with suspected VITT (previously VIPIT) are sent for testing by heparin-induced thrombocytopenia (HIT/VITT) ELISA and functional 'VITT' assays. Please refer to the most recent **THANZ VITT/VIPIT Advisory statement** for guidance on appropriate testing (https://www.thanz.org.au/).*

Patient Name: Last: _____ First: _____
Patient ID Number: _____ Sex: M ☐ / F ☐
Date of birth (DD-MMM-YYYY): _____
Sample Collection Date (DD-MMM-YYYY): _____ Collection Time: _____
Hospital/ clinic: _____
Ordering physician name: _____
Ordering physician phone number: _____
Fax for report: _____
Billing Address: _____

Sample requirements:	Separated serum from 4x red top (serum); AND
	Separated plasma 4x blue top (sodium citrate- plasma)

Sample Instructions	Please take plasma and serum samples PRIOR to IVIg therapy and anticoagulation. Treatment may result in false negatives.
	Separate serum and plasma into 500µL aliquots where possible. Ship frozen.
	Samples will need to be shipped as per the following instructions and include a copy of the completed form.

Samples will need to be shipped to these sites:

1. **NSW Referrals: send all sample aliquots (PLASMA and SERUM) for both ELISA and functional testing to:**

   Attn: VITT test samples, C/- Dr Vivien Chen
   Diagnostic Pathology unit
   Concord Repatriation General Hospital
   Hospital Road, CONCORD NSW 2139
   Tel: 02 9767 5892, Fax: 02 9767 8302

2. **Referrals from other Australian sites (all states other than NSW):**
   a. **Send 2 x serum aliquots to your local referral laboratory for ELISA VITT testing.** (Details on page 2).
   b. **Send the remaining SERUM sample aliquots and <u>all</u> PLASMA sample aliquots to:**

   VITT functional test samples
   Attn: Dr Vivien Chen
   Diagnostic Pathology unit - Coagulation laboratory
   Concord Repatriation General Hospital
   Hospital Road, CONCORD NSW 2139
   Tel: 02 9767 5892, Fax: 02 9767 8302

Lab testing in suspected VITT triaged according to information received

Australia and New Zealand VITT/VIPIT ELISA and functional testing request form

Please provide the following clinical information (missing clinical information may result in a delay in sample testing):

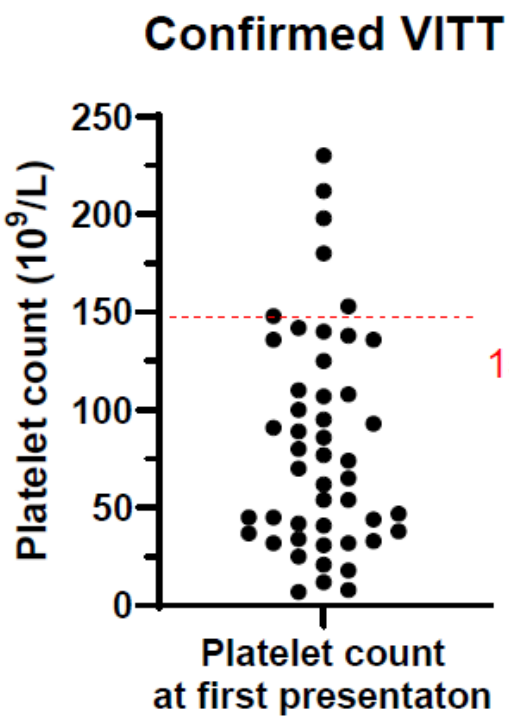
- Type of COVID-19 vaccine received:
  AstraZeneca ☐ Pfizer-BioNTech ☐ Other ☐ _____
  Date of 1st dose: _____ Date of 2nd dose: _____
- Presenting symptom(s): _____ Date of onset: _____
  _____
- Thrombosis: Yes ☐ No ☐ Date of thrombosis: _____
  a. Anatomical (arterial/venous/micro) sites of thrombosis (list all):
  _____
  b. List any alternative causes/recent provoking factors (e.g. surgery, OCP).
  _____
- Thrombocytopenia (count < 150 x 10^9/L): Yes ☐ No ☐
  a. Platelet count at sample collection: _____x10^9/L Platelet nadir: ____ x10^9/L
  b. List any alternative causes (including recent heparins - unfractionated or LMWH)?
  _____
- D-dimer result: _____ Upper limit of normal cut-off value: _____ Date of test: _____
- Fibrinogen level: _____ Date of test: _____
- Relevant medical history:
  Previous HIT ☐ Antiphospholipid syndrome ☐ Immune thrombocytopenia ☐
  Other ☐ _____
- Intravenous immunoglobulin therapy within the last 30 days? Yes ☐ No ☐
  Date of last dose: _____
- Recent heparin therapy? Yes ☐ No ☐
  Unfractionated ☐ Low molecular weight heparin ☐
  Date of last dose: _____

The following sites will receive samples for ELISA testing (list will be updated regularly):

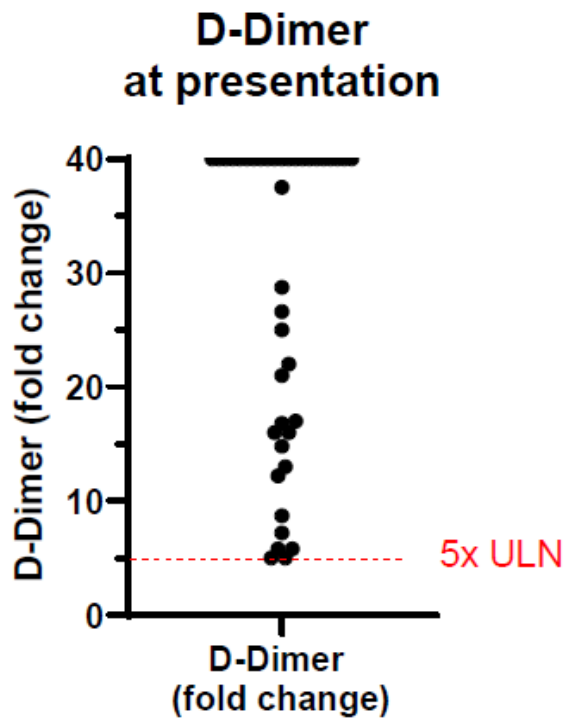
NSW	NSW Health Pathology - Concord Hospital Haematologist: Vivien Chen, Lisa Clarke
VIC	Monash Pathology – Monash Medical Centre Scientist: Joanne Clifford Haematologist: Sanjeev Chunilal
QLD	Pathology Queensland – Central pathology laboratory (Royal Brisbane) Scientist: Joanne Beggs, Leanne Ballard Haematologist: Bronwyn Williams
SA	SA Pathology, Royal Adelaide Hospital Scientists: Liz Duncan, Olivia Yacoub Haematologists: Chee Wee Tan, Yvonne Brennan
WA	PathWest Fiona Stanley Hospital Scientists: Matt Anderson, Lisa Kaminskis, Natasha Modica Haematologists: Stephanie P'ng, Dominic Pepperell

THANZ VITT/VIPIT Working Party Version 3.0 07/MAY/2021

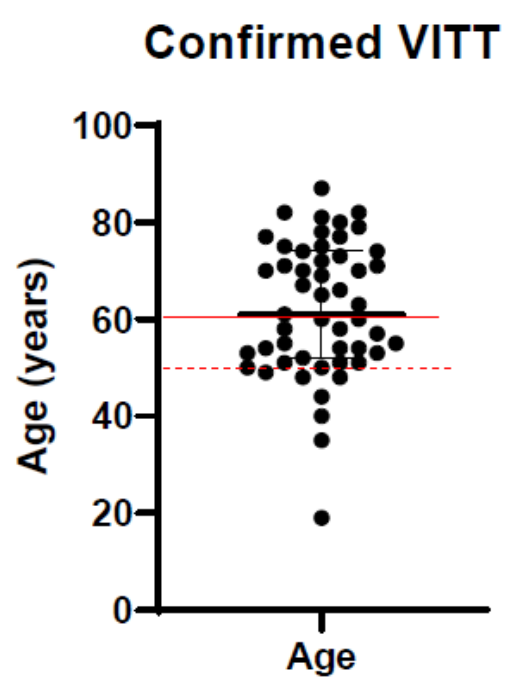
Australian VITT cases April 1-June 21
Platelet count and D-Dimer at first presentation

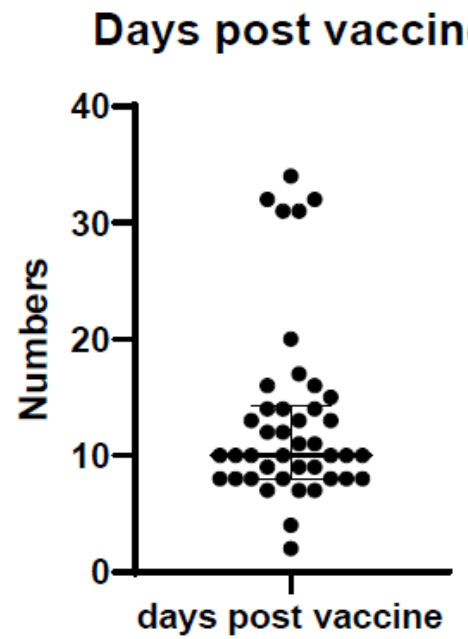


150 x 10^9/L



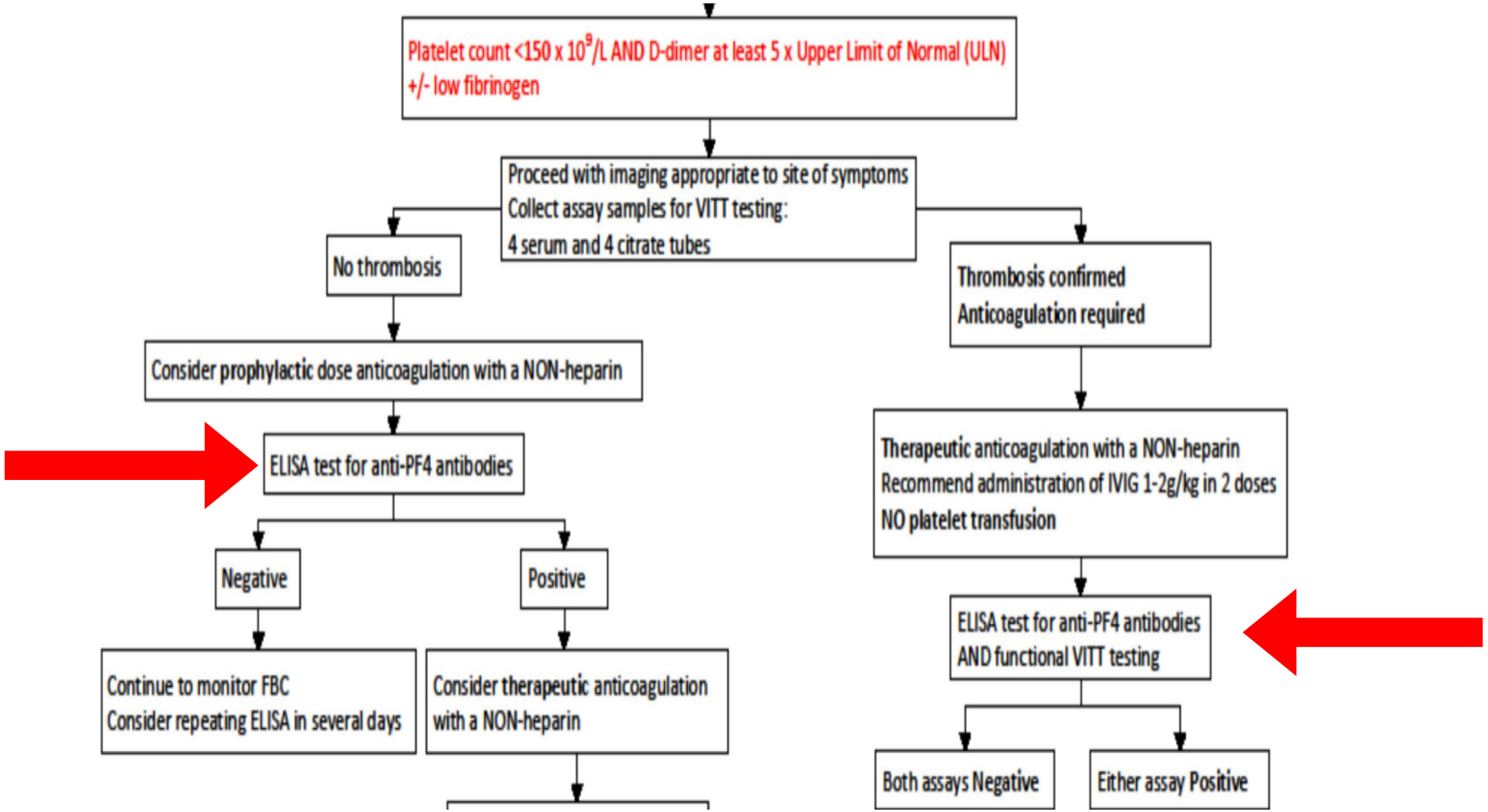
5x ULN





Note: these cases meet the criteria for **confirmed or strongly supported VITT** after specific testing according to THANZ criteria – they may not all have been adjudicated by TGA yet.

Second tier lab tests in suspected VITT



THANZ Advisory statement May 2021

Second tier lab tests in suspected VITT

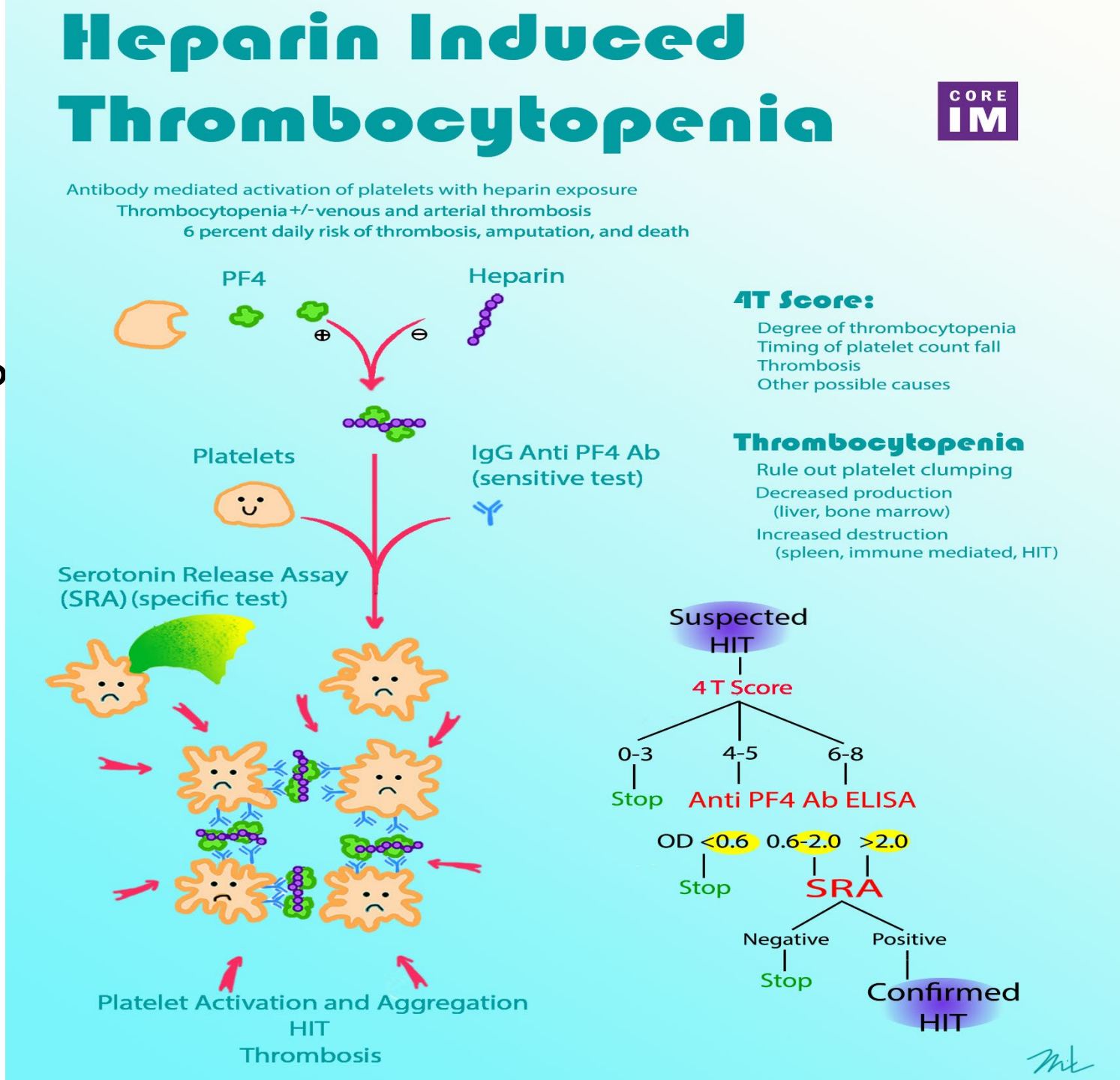
- Immunological assays for anti-platelet factor 4 (PF4) antibodies
- Only ELISA based assays seem to consistently identify anti-PF4 antibodies in suspected VITT
- Other rapid assays used to successfully identify anti-PF4/heparin antibodies in suspected HITT **do not** (in general) identify anti-PF4 antibodies in suspected VITT
- Important to identify samples as being for suspected VITT (vs for suspected HITT) in order to have correct tests performed
- If testing for suspected VITT not indicated or no VITT form, then HITT testing may be performed (potential false negative for VITT)

Poll 3. The following patients can receive AZ vaccine except

- Previous immune thrombocytopaenia
- Previous lower limb DVT
- Previous HITTs
- Previous antiphospholipid syndrome

HITTS

- 4T score high probability
- Positive Acustar for HITTs (anti-P
- Confirmed by Serotonin Release



NEJM – April 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination

Marie Scully, M.D., Deepak Singh, B.Sc., Robert Lown, M.D., Anthony Poles, M.D., Thomas Solomon, M.D., Marcel Levi, M.D., David Goldblatt, M.D., Ph.D., Pavel Kotoucek, M.D., William Thomas, M.D., and William Lester, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

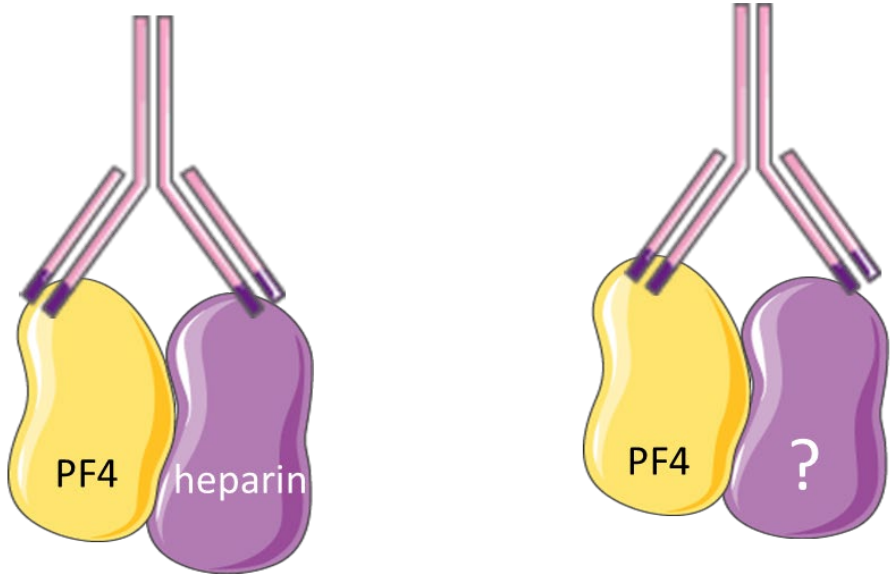
Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

BASIS OF HITT/VITT IMMUNOLOGICAL DIAGNOSTIC ASSAY

PF4 ELISA

HIT

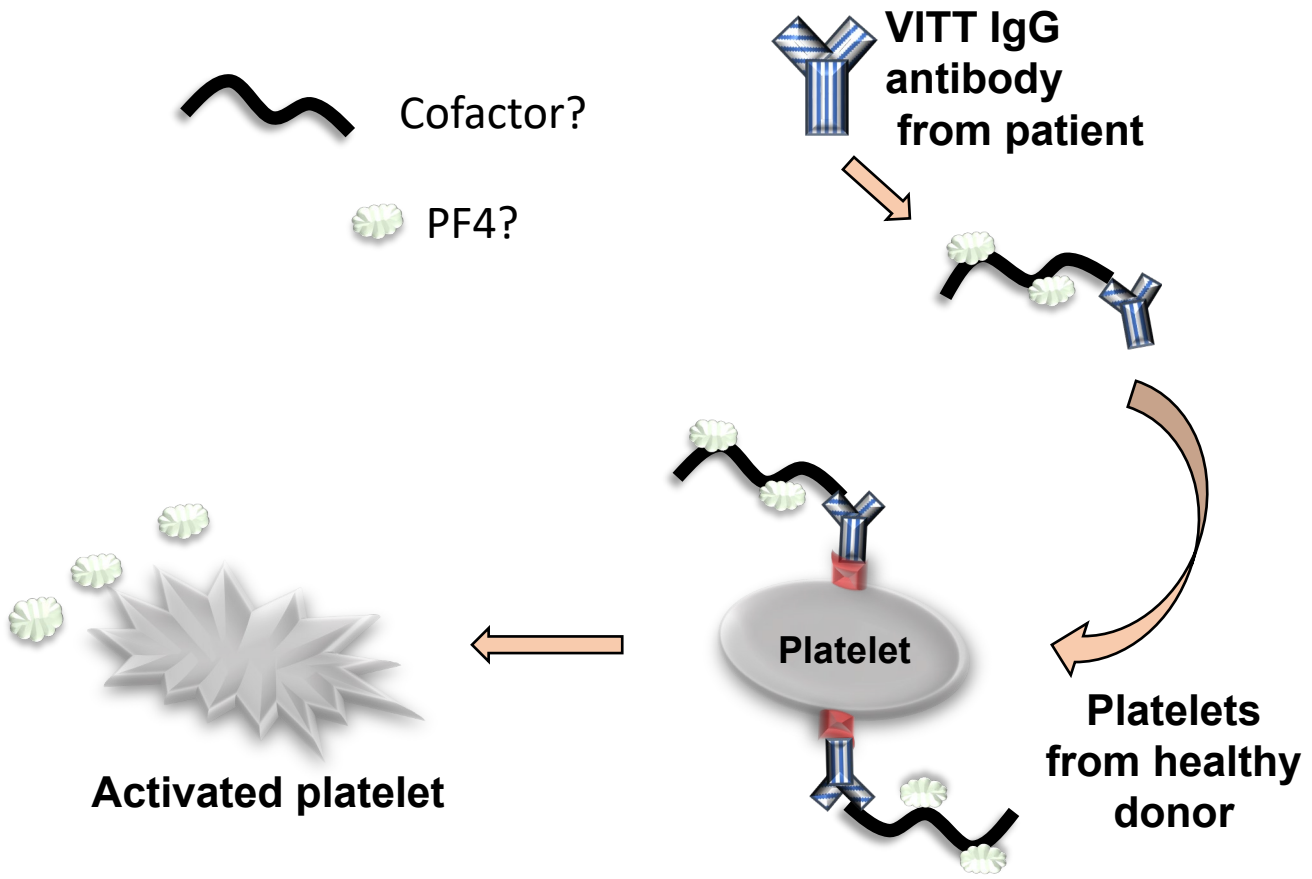
VITT

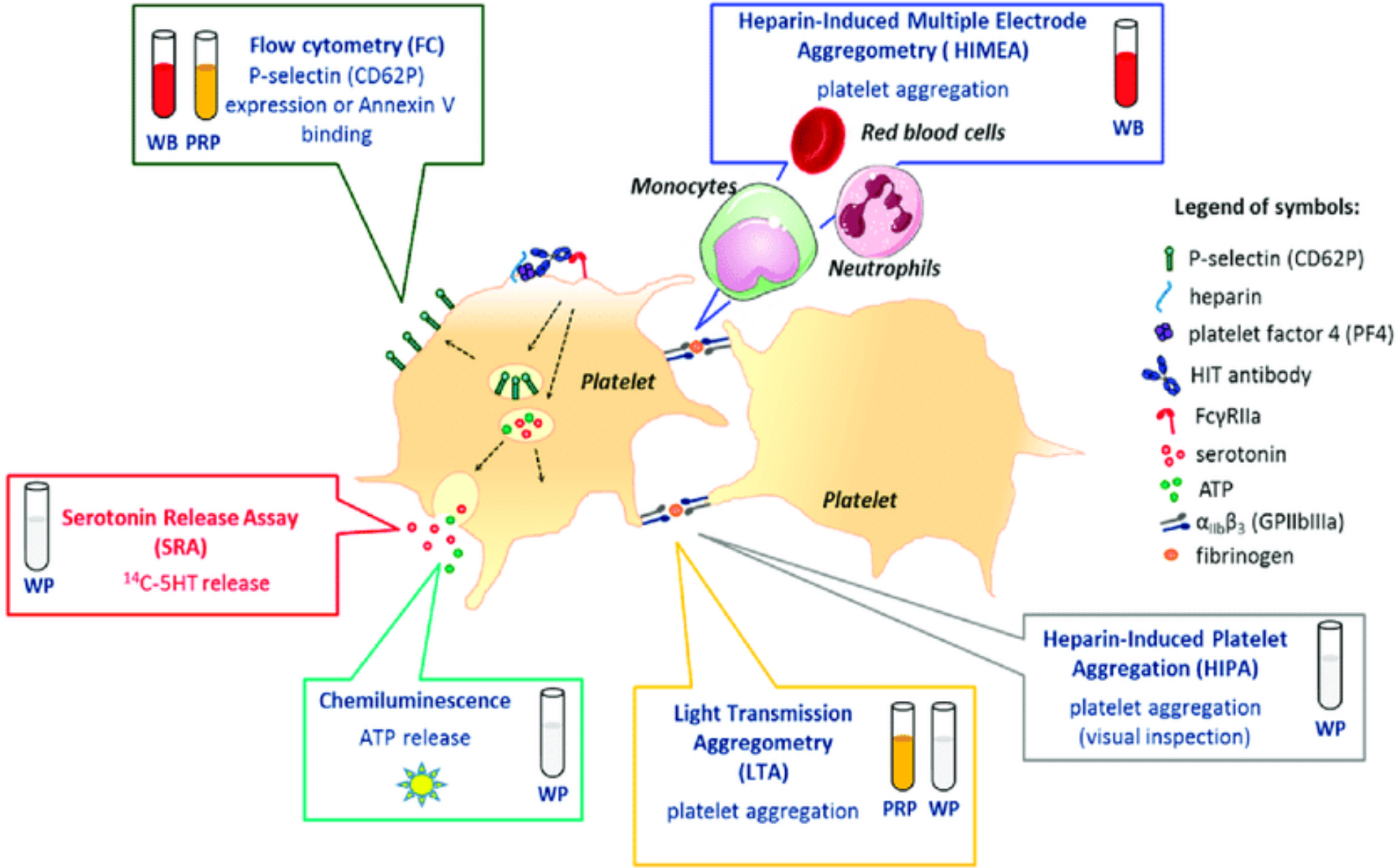


1:1

Different co-factor in VITT?

BASIS OF HITT/VITT FUNCTIONAL DIAGNOSTIC ASSAY




Flow cytometry (FC)
P-selectin (CD62P) expression or Annexin V binding
WB PRP
Heparin-Induced Multiple Electrode Aggregometry (HIMEA)
platelet aggregation
Red blood cells
WB
Monocytes
Neutrophils
Platelet
Platelet
Legend of symbols:
P-selectin (CD62P)
heparin
platelet factor 4 (PF4)
HIT antibody
FcγRIIa
serotonin
ATP
$\alpha_{IIb}\beta_3$ (GPIIbIIIa)
fibrinogen
Serotonin Release Assay (SRA)
^{14}C-5HT release
WP
Chemiluminescence
ATP release
WP
Light Transmission Aggregometry (LTA)
platelet aggregation
PRP WP
Heparin-Induced Platelet Aggregation (HIPA)
platelet aggregation (visual inspection)
WP

Poll 4.My patient has previous HITTS after CABG 11 years ago, so the recommendation should be ….

- Retest for HITTS prior to vaccine discussion
- Offer AZ vaccine
- Offer Pfizer
- Don’t offer either vaccine
- Can offer Pfizer but only after first dose AZ vaccine

Comirnaty (Pfizer) is recommended for people 16 years and above with:

- A past history of cerebral venous sinus thrombosis (CVST)
- A past history of heparin-induced thrombocytopenia (HIT)
- A past history of idiopathic splanchnic (mesenteric, portal and splenic) venous thrombosis
- Anti-phospholipid syndrome with thrombosis
- People with contraindications to COVID-19 Vaccine AstraZeneca, i.e.
  - Anaphylaxis to a previous dose of COVID-19 Vaccine AstraZeneca, or to an ingredient of the vaccine
  - Thrombosis with thrombocytopenia occurring after the first dose of COVID-19 Vaccine AstraZeneca
  - Other serious adverse events attributed to the first dose of COVID-19 Vaccine AstraZeneca

Poll 5.62 year old male who had PE post TKR two years ago. He is overweight and has diabetes. He wants Pfizer as AZ vaccine increases his risk of clots

True

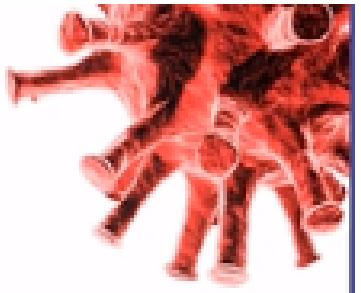
False

Neither

AZ Vaccine for……

- The risk of TTS is not likely to be increased in people with the following conditions, and people in these groups can receive COVID-19 Vaccine AstraZeneca:
  - History of blood clots in typical sites
  - Increased clotting tendency that is not immune mediated
  - Family history of blood clots
  - History of ischaemic heart disease or stroke
  - Current or past thrombocytopenia (low platelet count)
  - Those receiving anticoagulation therapy

To put some risks into perspective



- Thrombosis and pulmonary embolism: 2 per 1000 per year[1]
- Cerebral venous thrombosis: 2 to 3 per 100,000 per year[2]
- Oral contraceptives: 5 per 10,000 young women (aged 20–30) per year[3]
- Pregnancy: 1 to 2 per 1000[3]
- Air travel: 1 per 4600 flights (>4 hours)[4]

MAT-GLB-2101946(V1.0) June 2021

1. Naess IA, *et al. J Thromb Haemost*. 2007;5(4):692–9; 2. Coutinho JM, *et al. Stroke*. 2012;43:3375–7; 3. Bleker SM, *et al. Blood Rev*. 2014;28(3):123–33; 4. Kuipers S, *et al. J Intern Med*. 2007;262(6):615–34

Poll 6. 65-yr old who in her thirties had pregnancy loss due to suspected Lupus Anticoagulant. No other history of thrombosis.

- She should be offered AZ vaccine
- She should be offered the Pfizer vaccine
- She should have neither

Poll 7. 71 year old with cirrhosis due to NASH and history of prostate cancer on hormone therapy. He has a past history of cirrhosis associated portal vein thrombosis.

- He should be offered AZ vaccine
- He should be offered the Pfizer vaccine
- He should have neither

Pfizer is preferred for

- The list of conditions for which Comirnaty (Pfizer) is the preferred vaccine has been expanded to also include:
  - Past history of idiopathic splanchnic (mesenteric, portal, splenic) vein thrombosis
  - Antiphospholipid syndrome with thrombosis

APLS and thrombosis

APLS criteria with clearly documented **VTE or arterial clots**

C – H I A R O – D –

Critical to identify as Idiopathic thrombosis for splanchnic

Poll 8. My patient who is 75 yrs has CLL and moderate thrombocytopaenia with plts 90x 10^9/L… He also has ischemic heart disease and is on aspirin

- I will need to request Pfizer for this patient
- I can proceed with AZ whilst closely monitoring platelet counts
- Cannot be vaccinated as they have a cancer and low platelets
- Patient preference is not to have vaccination so will support that

AZ Vaccine for……

- The risk of TTS is not likely to be increased in people with the following conditions, and people in these groups can receive COVID-19 Vaccine AstraZeneca:
  - History of blood clots in typical sites
  - Increased clotting tendency that is not immune mediated
  - Family history of blood clots
  - History of ischaemic heart disease or stroke
  - Current or past thrombocytopenia (low platelet count)
  - Those receiving anticoagulation therapy

This includes antiplatelets and anticoagulants

ITP and COVID-19 vaccines

- Natural history of ITP is very variable
- Thrombocytopaenia can occur with both mRNA and adenoviral vector vaccines
- Risk of ITP is low with either vaccine
- https://www.itpsupport.org.uk/images/downloads/FAQs_ITP_and_C-19_vaccination_04012020.pdf

Poll 9.My 67 yr old patient had an extensive left leg DVT after AZ vaccine, did not meet criteria for VITT. Should she get a second dose of AZ?

- I would prefer not to vaccinate the second dose
- I will request a second dose alternative e.g. Pfizer
- Cannot be vaccinated for 3 months as patient will be on anticoagulant
- Thrombophilia testing is pending so prefer to wait for those results

Comirnaty (Pfizer) is recommended for people 16 years and above with:

- A past history of cerebral venous sinus thrombosis (CVST)
- A past history of heparin-induced thrombocytopenia (HIT)
- A past history of idiopathic splanchnic (mesenteric, portal and splenic) venous thrombosis
- Anti-phospholipid syndrome with thrombosis
- People with contraindications to COVID-19 Vaccine AstraZeneca, i.e.
  - Anaphylaxis to a previous dose of COVID-19 Vaccine AstraZeneca, or to an ingredient of the vaccine
  - Thrombosis with thrombocytopenia occurring after the first dose of COVID-19 Vaccine AstraZeneca
  - Other serious adverse events attributed to the first dose of COVID-19 Vaccine AstraZeneca

Poll 10. My 68 yr old retired engineer patient wants a discussion on risks and benefits of the vaccine in relation to TTS as he has a family history of clots?

I know where to find the stats and support for him

I do not know where to find them and how to support him

Low risk situation

Scenario 1: Infection rate similar to first wave of COVID-19 in Australia (29 infections per 100,000 people in a 16-week period)

For every 100,000 AstraZeneca vaccinations

Age	Potential harms Australian data as at 16 June 2021	Potential benefits
18–29	1.9 blood clots (TTS)[a]	0.0 deaths prevented 0.1 ICU admissions prevented 1.0 hospitalisations prevented
30–39	1.6 blood clots (TTS)[a]	0.0 deaths prevented 0.5 ICU admissions prevented 1.9 hospitalisations prevented
40–49	5.0 blood clots (TTS)[a]	0.0 deaths prevented 0.8 ICU admissions prevented 2.6 hospitalisations prevented
50–59	2.7 blood clots (TTS)	0.1 deaths prevented 1.4 ICU admissions prevented 4.6 hospitalisations prevented
60–69	1.4 blood clots (TTS)	0.4 deaths prevented 2.1 ICU admissions prevented 7.2 hospitalisations prevented
70–79	1.8 blood clots (TTS)	1.5 deaths prevented 3.4 ICU admissions prevented 8.8 hospitalisations prevented
80+	1.9 blood clots (TTS)	6.2 deaths prevented 1.6 ICU admissions prevented 11.5 hospitalisations prevented

TTS = thrombosis with thrombocytopenia syndrome

Weighing up risks and benefits

Scenario 1: Low exposure risk – infection rate similar to first wave of COVID-19 in Australia (29 infections per 100,000 people in a 16-week period)

For every 100,000 people vaccinated				
Age group	Cases of TTS due to COVID-19 Vaccine AstraZeneca	Hospitalisations prevented	ICU admissions prevented	Deaths prevented
18–29 years	1.9[a]	1.0	0.1	0.0
30–39 years	1.6[a]	1.9	0.5	0.0
40–49 years	5.0[a]	2.6	0.8	0.0
50–59 years	2.7	4.6	1.4	0.1
60–69 years	1.4	7.2	2.1	0.4
70–79 years	1.8	8.8	3.4	1.5
≥80 years	1.9	11.5	1.6	6.2

TTS = thrombosis with thrombocytopenia syndrome

a Estimates of risk are uncertain as rates are based on small numbers of vaccinations in people under 50 in Australia.

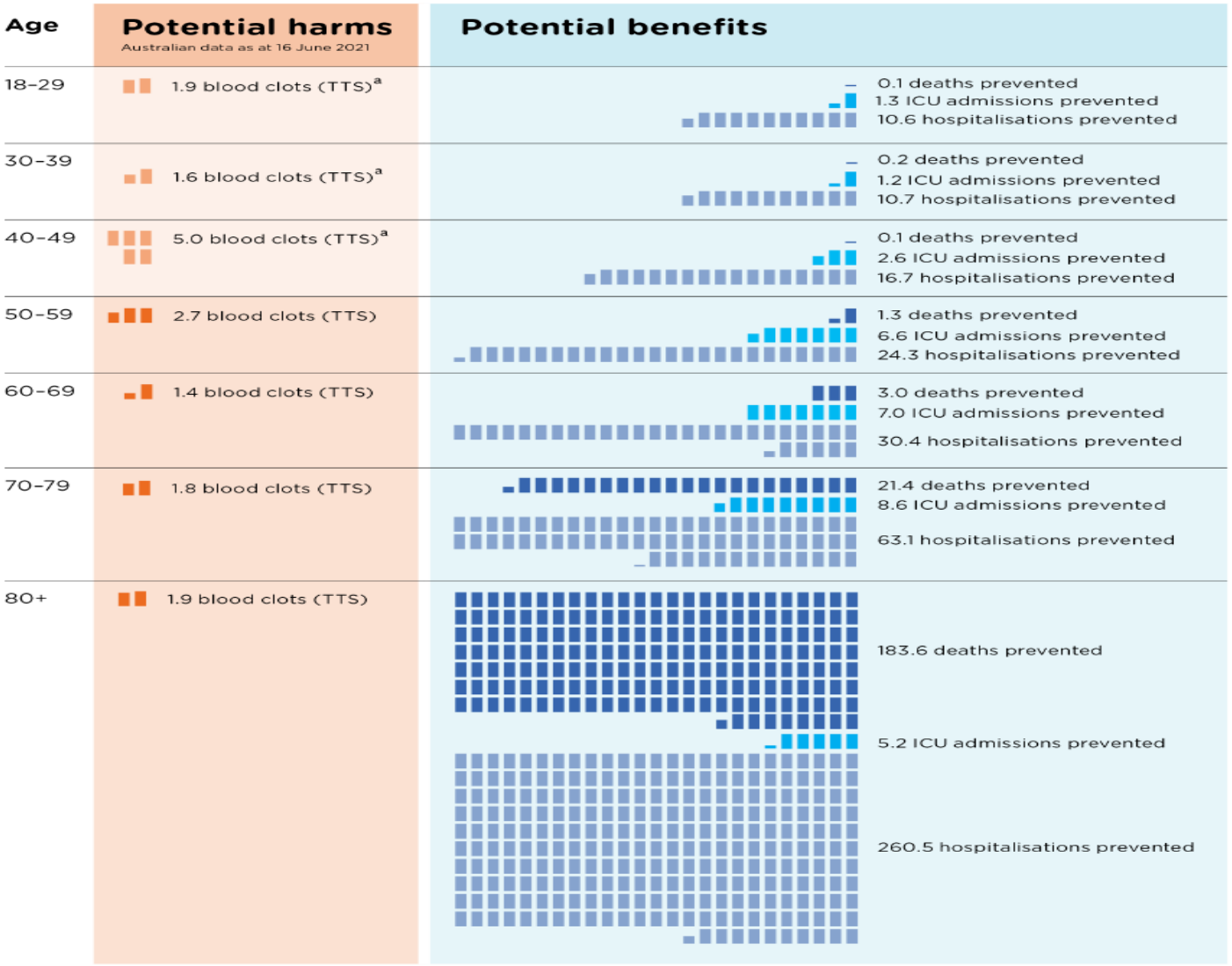
Note: Potential benefits calculated from confirmed data from ACT, NSW, Tasmania and Victoria.

ATAGI June 2021

Scenario 2: Infection rate similar to second wave of COVID-19 in Victoria (275 infections per 100,000 people in a 16-week period)

Medium risk

For every 100,000 AstraZeneca vaccinations



TTS = thrombosis with thrombocytopenia syndrome
a Estimates of risk are uncertain as rates are based on small numbers of vaccinations in people under 50 in Australia

Weighing up risks and benefits …2

Scenario 2: Medium exposure risk – infection rate similar to second wave of COVID-19 in Victoria (275 per 100,000 people in a 16-week period)

For every 100,000 people vaccinated				
Age group	Cases of TTS due to COVID-19 Vaccine AstraZeneca	Hospitalisations prevented	ICU admissions prevented	Deaths prevented
18–29 years	1.9[a]	10.6	1.3	0.1
30–39 years	1.6[a]	10.7	1.2	0.2
40–49 years	5.0[a]	16.7	2.6	0.1
50–59 years	2.7	24.3	6.5	1.3
60–69 years	1.4	30.4	7.0	3.0
70–79 years	1.8	63.1	8.6	21.4
≥80 years	1.9	260.5	5.2	183.6

TTS = thrombosis with thrombocytopenia syndrome

a Estimates of risk are uncertain as rates are based on small numbers of vaccinations in people under 50 in Australia.

Note: Potential benefits calculated from confirmed data from Victoria.

ATAGI June 2021

Weighing up risks and benefits …..3

Scenario 3: High exposure risk – infection rate based on data from Europe in January 2021 (3,544 infections per 100,000 people in a 16-week period)

For every 100,000 people vaccinated				
Age group	Cases of TTS due to COVID-19 Vaccine AstraZeneca	Hospitalisations prevented	ICU admissions prevented	Deaths prevented
18–29 years	1.9[a]	64	6	0
30–39 years	1.6[a]	81	8	3
40–49 years	5.0[a]	122	15	10
50–59 years	2.7	208	28	14
60–69 years	1.4	324	50	45
70–79 years	1.8	547	78	172
≥80 years	1.9	1239	110	733

TTS = thrombosis with thrombocytopenia syndrome

a Estimates of risk are uncertain as rates are based on small numbers of vaccinations in people under 50 in Australia.

Note: Potential benefits calculated from confirmed data from Europe.

ATAGI June 2021

Age	Total cases	CDC classification†		
		Tier 1	Tier 2	Not classified
<30 years	1	-	1	-
30-39	1	1	-	-
40-49	4	4	-	-
50-59	20	9	6	5
60-69	13	3	4	6
70-79	19	6	5	8
80+	11	3	4	4
All ages	**69** **(34 men, 35 women)**	26	20	23

† The US CDC classification is defined as:

- Tier 1 = clots in an unusual location (such as the brain or abdomen) **and** a low platelet count with or without antibodies that activate platelets (anti-PF4 antibodies)
- Tier 2 = clots found in common locations (such as the leg or lungs) and a low platelet count **and** anti-PF4 antibodies
- Not classified = case does not meet the criteria for Tier 1 or Tier 2 (for example clots in common locations with **low** platelet count but no evidence of anti-PF4 antibodies).

Table 3: Time to onset, treatment and outcomes for TTS cases*

Time to onset/ diagnosis (days)	Median (range)	12 (1-44)
Treated in ICU	At any point†	18
	Currently	3
Outcome	Discharged	51
	In hospital	16
	Fatal	2

Source TGA 06 July 2021

Resources… use up to date links on websites

- https://www.tga.gov.au/covid-19-vaccine-information-consumers-and-health-professionals
- https://www.tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-01-07-2021

- https://www.health.gov.au/news/atagi-statement-on-revised-recommendations-on-the-use-of-covid-19-vaccine-astrazeneca-17-june-2021
- https://www.health.gov.au/news/joint-statement-from-atagi-and-thanz-on-thrombosis-with-thrombocytopenia-syndrome-tts-and-the-use-of-covid-19-vaccine-astrazeneca
- https://www.health.gov.au/sites/default/files/documents/2021/06/covid-19-vaccination-weighing-up-the-potential-benefits-against-risk-of-harm-from-covid-19-vaccine-astrazeneca_2.pdf

NSW Health safety notice July 2021

NSW GOVERNMENT

Safety Notice 013/21

Changes to COVID-19 vaccine access and indications (updated)

1 July 2021

Distributed to:
- Chief Executives
- Directors of Clinical Governance
- Directors of Public Health

Action required by:
- Chief Executives
- Directors of Clinical Governance
- Medical Staff
- Public Health Units
- Immunisation Staff.

We recommend you also inform:

LHD staff involved in delivering vaccination

Directors of:
- Emergency Departments
- Intensive Care Units
- Surgery
- General Medicine
- Cardiology
- Respiratory medicine
- Haematology
- Neurology

Expert Reference Group

Content reviewed by:
- NSW Health Public Health Response Branch

Clinical Excellence Commission

Tel: 02 9269 5500

Fax: 02 9269 5599

Email: CEC-Recalls@health.nsw.gov.au

Internet Website: http://health.nsw.gov.au/sabs

Intranet Website: http://internal.health.nsw.gov.au/quality/sabs

Review date

1 August 2021

Updated advice regarding choice of COVID-19 vaccines

On Thursday 17 June the Australian Technical Advisory Group on Immunisation (ATAGI) provided updated advice that Pfizer is the preferred COVID-19 vaccine for people **under 60 years**. On 29 June, the Australian Government announced that people under 60 years of age can access the COVID-19 Vaccine AstraZeneca through their GP, with fully informed consent. Clinicians should be alert to the **possibility of adverse events in people aged less than 60 following COVID-19 AstraZeneca vaccination**.

Pfizer COMIRNATY® COVID-19 vaccine is recommended for:
- People under 60 years
- People with a history of cerebral venous sinus thrombosis (CVST)
- People with a history of heparin-induced thrombocytopenia (HIT)
- People with a history of splanchnic (mesenteric, portal, splenic) vein thrombosis
- Patients with anti-phospholipid syndrome with thrombosis
- People with contraindications to COVID-19 Vaccine AstraZeneca, such as:
  - Anaphylaxis to a previous dose of COVID-19 Vaccine AstraZeneca, or to an ingredient of the vaccine
  - Thrombosis with thrombocytopenia after the first dose of COVID-19 Vaccine AstraZeneca
  - Other serious adverse events attributed to the first dose of COVID-19 Vaccine AstraZeneca (these events should be reported to the local Public Health Unit. A specialist service is available to support clinical decision making and advice)

ATAGI advises the following can continue to receive AstraZeneca:

People aged 60 years and older (other than those with conditions above), including:
- People with a history of venous thromboembolism in typical sites, such as deep vein thrombosis or pulmonary embolism
- People with other predisposition to form blood clots, such as those with Factor V Leiden, or other non-immune thrombophilic disorders
- People with a family history of clots or clotting conditions
- People currently receiving anticoagulant medications
- People with a history of ischaemic heart disease or cerebrovascular accident
- People with a current or past history of thrombocytopenia (low platelet count).

ATAGI reinforces that people of any age who have had their first dose of COVID-19 Vaccine AstraZeneca without any serious adverse events can receive the second dose.

Access to Pfizer COMIRNATY® COVID-19 vaccination
- Patients who receive medical advice that Pfizer is preferred for them should regularly check the COVID-19 vaccine eligibility checker and monitor the 'clinic booking' link as local availability of the Pfizer COVID-19 vaccine may change
- LHDs should refer patients requiring clinical assessment regarding vaccine suitability to their local Pfizer vaccination clinic or GP
- Patients under 60 years can access Pfizer vaccine at a NSW Health clinic through the vaccine eligibility checker.

Suggested actions required by Local Health Districts/Networks

1. Ensure clinicians are aware of updated advice regarding COVID-19 vaccines
2. Remind clinicians to be alert to possible suspected adverse events following COVID-19 vaccination, and report to the local public health unit on **1300 066 055**.

Resources within NSW

NSW GOVERNMENT

Safety Notice 013/21

1 July 2021

Changes to COVID-19 vaccine access and indications (updated)

Specialist immunisation advice

If specialist advice is needed, for example in relation to providing the second dose of vaccine, contact the National Centre for Immunisation Research and Surveillance (NCIRS) NSW Immunisation Specialist Service (NSWISS)

☏ Phone: 1800 679 477 (Mon-Fri 9am-5pm) **OR**
✉ Email: SCHN-NSWISS@health.nsw.gov.au

For urgent after-hours clinical support, contact NSWISS via The Children's Hospital at Westmead switchboard on ☏ 02 9845 0000

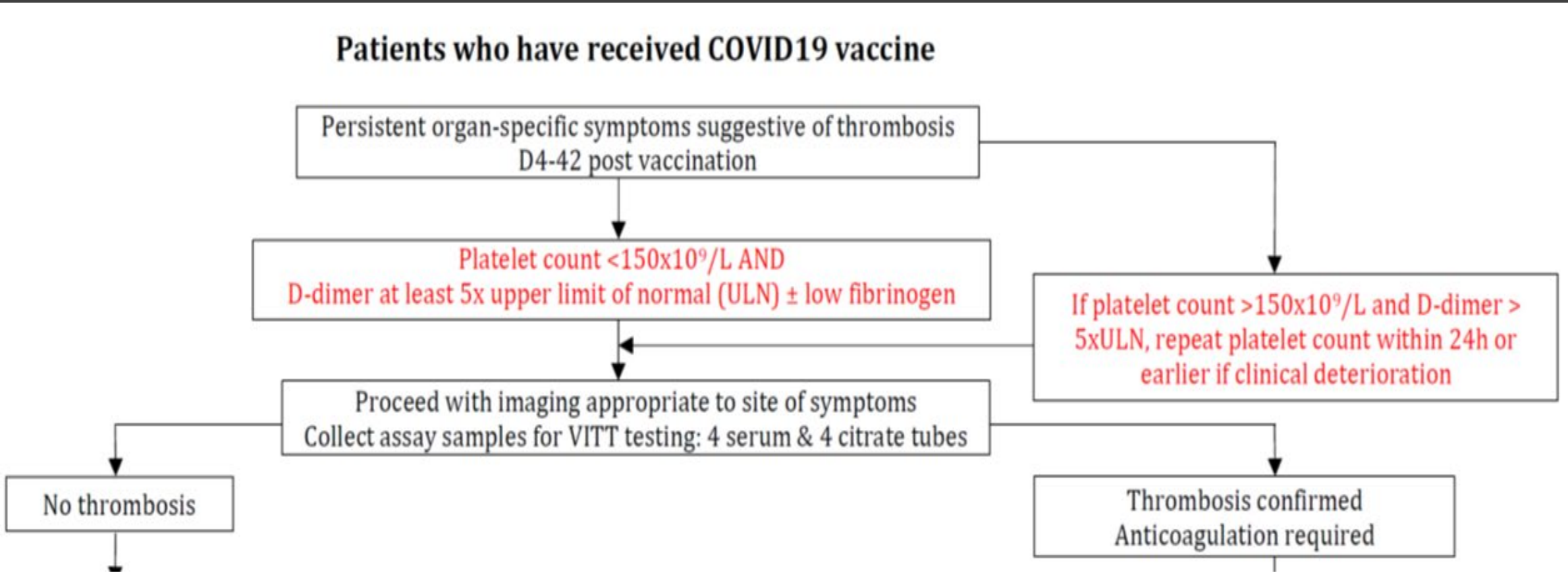
Contraindications and precautions to immunisation with COVID-19 vaccines

It is important that patients are provided with the latest advice regarding which COVID-19 vaccine is recommended. Latest information for clinicians is available at https://www.health.nsw.gov.au/Infectious/covid-19/vaccine/Pages/clinicians.aspx. This advice changes regularly as additional information around vaccine safety becomes available.

Where clinical advice is required regarding interpretation of this advice please contact the National Centre for Immunisation Research and Surveillance (NCIRS) NSW Immunisation Specialist Service (NSWISS).

Can TTS be recognised early ?

Updated THANZ document in progress



THANZ

SCAN ME

#Link to VITT Testing Form

*Symptoms/signs:

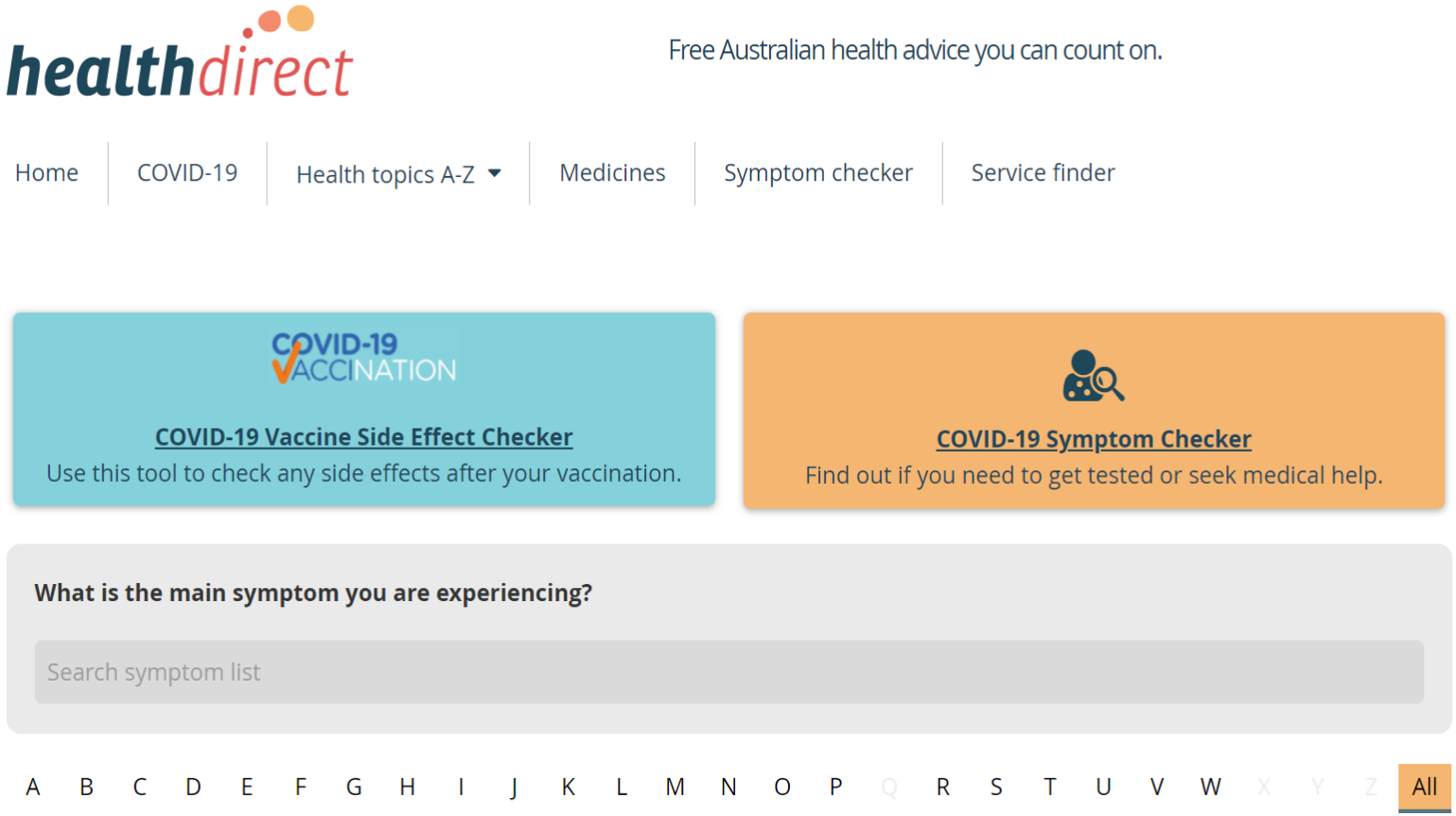
CVT: persistent headache, visual changes, focal neurological symptoms, seizures, coma, secondary ICH
Splanchnic vein thrombosis: abdominal pain
PE/DVT: chest pain, dyspnoea, leg pain, redness or swelling
Arterial ischaemia: pallor and coldness in limb, myocardial ischaemia
Thrombocytopenia: petechiae, acute onset bruising or bleeding

§ **If normal platelet count and d-dimer ≥ 5 x ULN with persisting symptoms, consider repeat FBC and/or imaging**

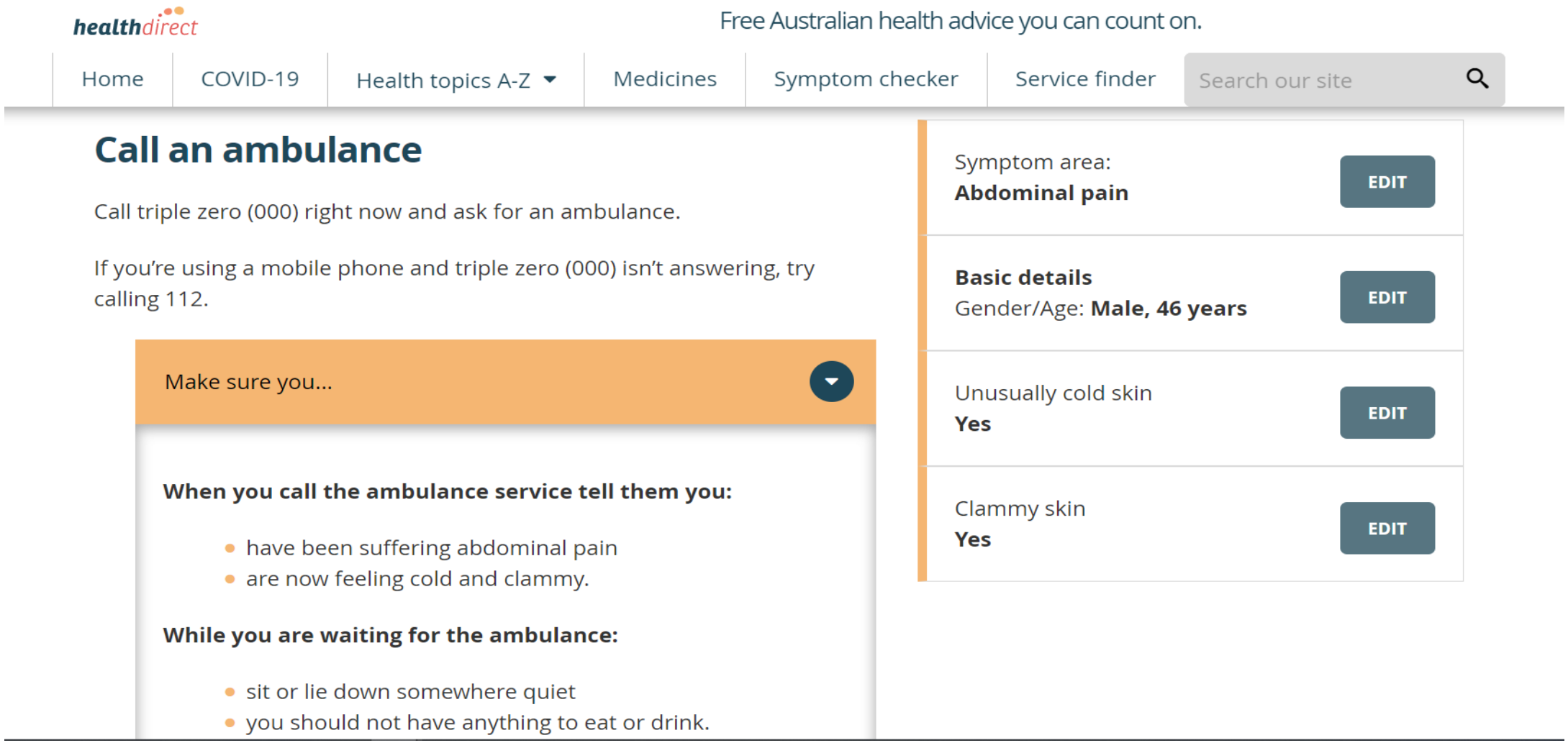
SCAN ME

Link to THANZ Advisory Statement

COVID-19 vaccine side effect tracker



Symptom tracker



Aim: To make VITT a manageable complication rather than a vaccine limiting one

- Treatable condition
- Awareness of diagnostic and treatment pathways
- Recognising pattern of screening tests
- Weighing up risks and benefits pragmatically

QUESTIONS please post

THANK YOU

ACKNOWLEDGEMENTS

Local, national and international collaborators

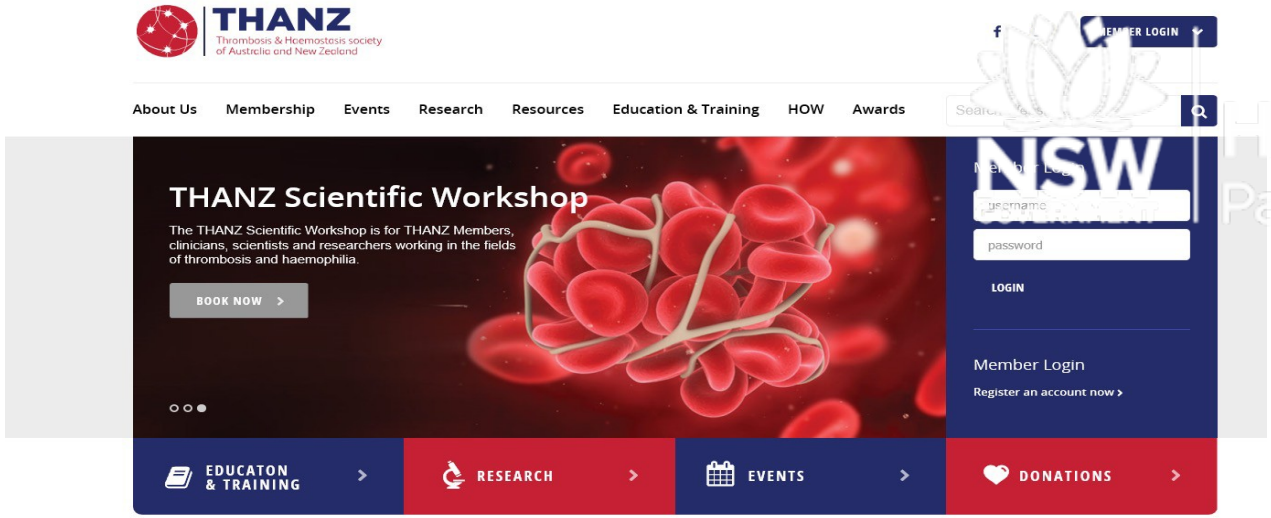
THANZ VITT advisory group led by A/Prof Vivien Chen

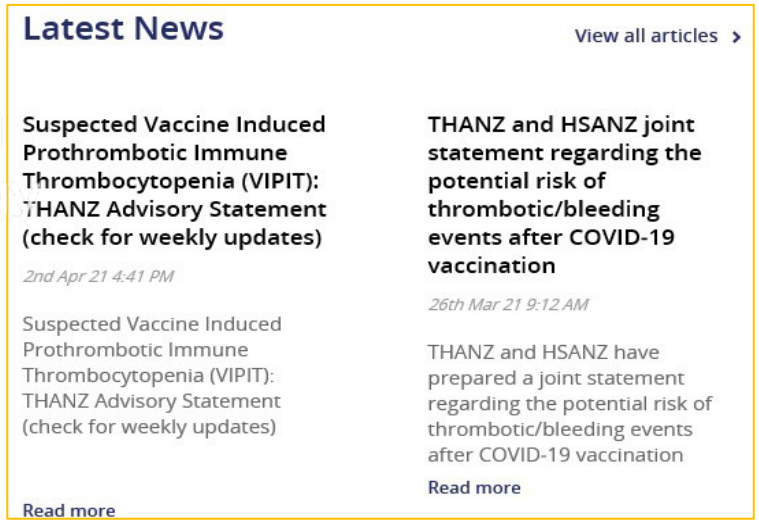
VITT ELISA group led by Dr Emannuel Favaloro

Public health, NSW Health, ATAGI and TGA

Please refer to theTHANZ website which is updated weekly - https://www.thanz.org.au/

Anoop.Enjeti@calvarymater.org.au





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NSW GOVERNMENT Health Pathology