Thrombosis with Thrombocytopaenia Syndrome (TTS) in Australia [2021]
Clinical and epidemiological features

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The first known case of vaccine-induced thrombotic thrombocytopenia in Australia

Jay Hocking, Sanjeev D Chunilal, Vivien M Chen, Tim Brighton, James Nguyen, Jocelyn Tan, Stephen B Ting and Huyen Tran

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A health care worker presented with fevers, fatigue and head “fogginess” with abdominal discomfort and increased bowel frequency 8 days after receiving his first dose of the COVID-19 vaccine (ChAdOx1-S [recombinant]) (AstraZeneca).

[MJA 1st case confirmed VITT in Australia, April 2021]

Australian Government
Department of Health

Home | Health topics | Initiatives and programs | Resources

Home › Initiatives and programs › COVID-19 vaccines › Advice for COVID-19 vaccine providers and administrators › ATAGI clinical guidance for COVID-19 vaccine providers

Vaxzevria (AstraZeneca) vaccine and thrombosis with thrombocytopenia (TTS)

Clinical advice on the AstraZeneca vaccine and thrombosis with thrombocytopenia (TTS).

[TTS Australian clinical guidance]

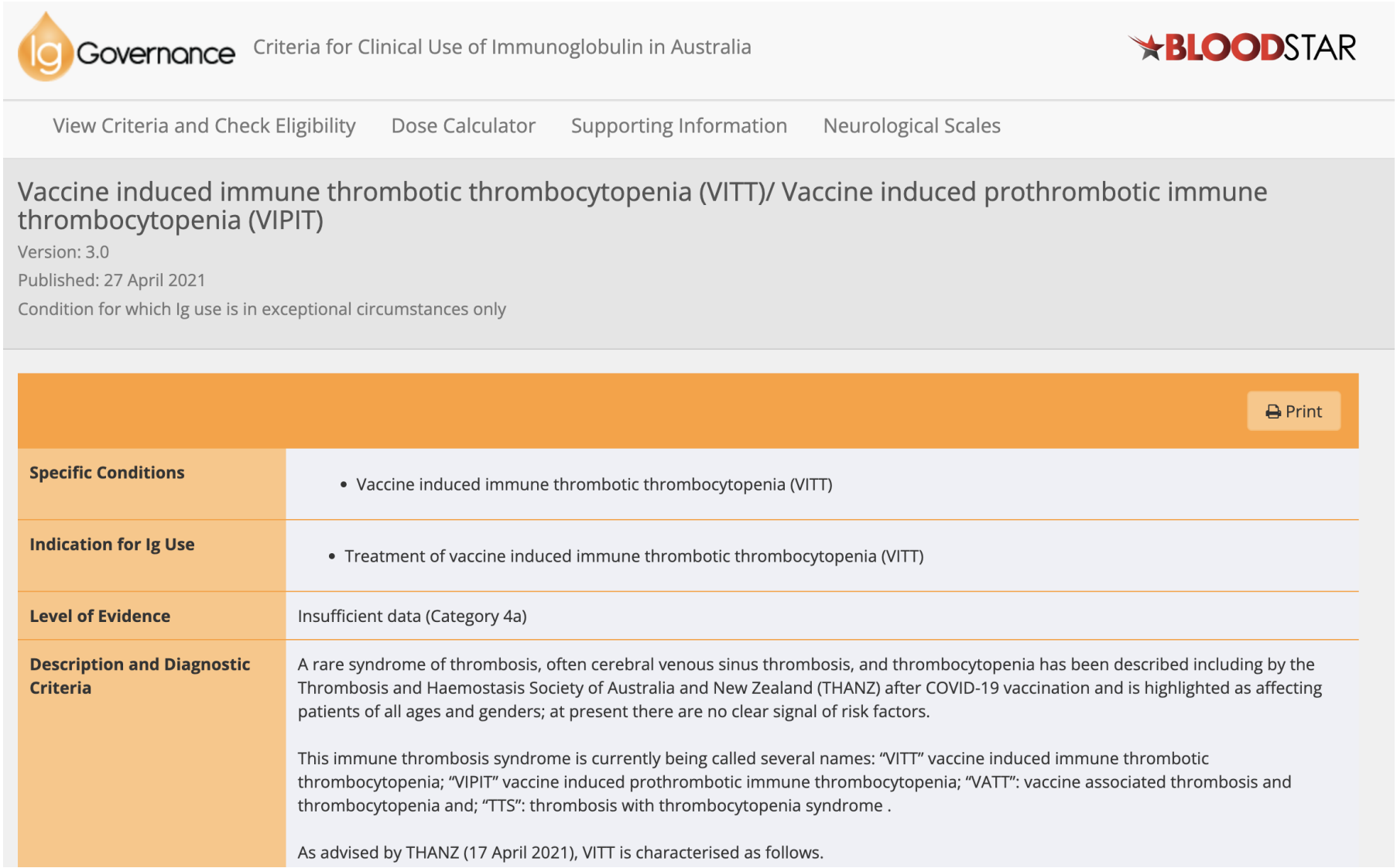
Low exposure risk in the Australian context

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 early case identification and treatment



Governance Criteria for Clinical Use of Immunoglobulin in Australia

BLOODSTAR

View Criteria and Check Eligibility | Dose Calculator | Supporting Information | Neurological Scales

Vaccine induced immune thrombotic thrombocytopenia (VITT)/ Vaccine induced prothrombotic immune thrombocytopenia (VIPIT)

Version: 3.0

Published: 27 April 2021

Condition for which Ig use is in exceptional circumstances only

Print

Specific Conditions	• Vaccine induced immune thrombotic thrombocytopenia (VITT)
Indication for Ig Use	• Treatment of vaccine induced immune thrombotic thrombocytopenia (VITT)
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	A rare syndrome of thrombosis, often cerebral venous sinus thrombosis, and thrombocytopenia has been described including by the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) after COVID-19 vaccination and is highlighted as affecting patients of all ages and genders; at present there are no clear signal of risk factors. This immune thrombosis syndrome is currently being called several names: "VITT" vaccine induced immune thrombotic thrombocytopenia; "VIPIT" vaccine induced prothrombotic immune thrombocytopenia; "VATT": vaccine associated thrombosis and thrombocytopenia and; "TTS": thrombosis with thrombocytopenia syndrome . As advised by THANZ (17 April 2021), VITT is characterised as follows.

https://www.criteria.blood.gov.au/MedicalCondition/View/2669

Australian Confirmed and probable TTS cases by state and territory

		By vaccine dose		By TGA classification	
Jurisdiction	All **N=171**	Dose 1 N=147	Dose 2 N=24	Confirmed N=88	Probable N=83
ACT	1 (0.6%)	1 (0.7%)	0 (0%)	0 (0%)	1 (1.2%)
NSW	77 (45%)	59 (40%)	18 (75%)	32 (36%)	45 (54%)
QLD	20 (12%)	18 (12%)	2 (8.3%)	11 (12%)	9 (11%)
SA	7 (4.1%)	7 (4.8%)	0 (0%)	4 (4.5%)	3 (3.6%)
TAS	2 (1.2%)	2 (1.4%)	0 (0%)	2 (2.3%)	0 (0%)
VIC	51 (30%)	48 (33%)	3 (12%)	29 (33%)	22 (27%)
WA	13 (7.6%)	12 (8.2%)	1 (4.2%)	10 (11%)	3 (3.6%)

*1 additional case from the Northern Territory

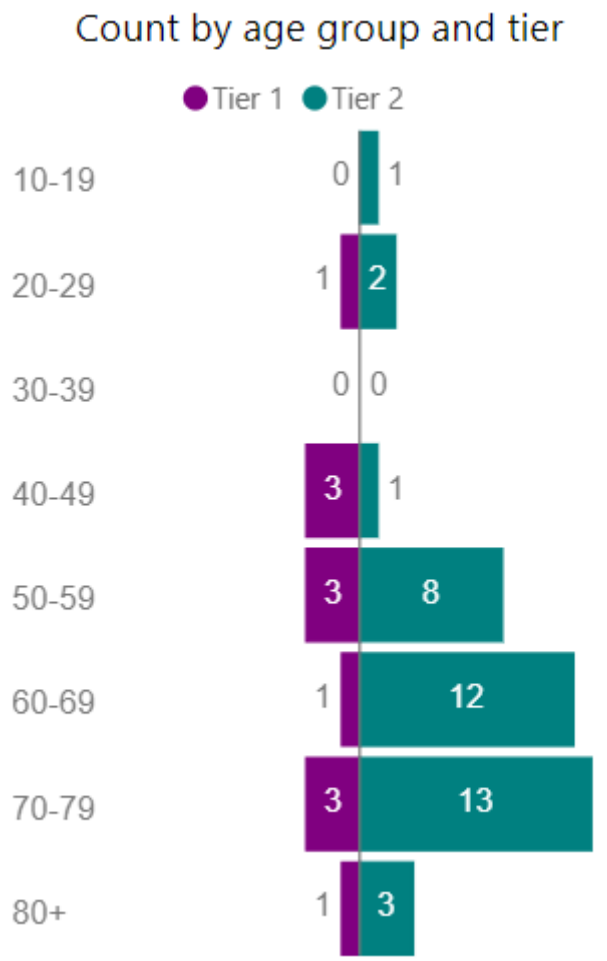
Slide acknowledgement: AusVaxSafety (NCIRS): Nick Wood and Lucy Deng

Clinical presentation and investigations (Victoria: n=51)

- Age range: 19 to 94 years
- Sex: M:F, 1:1

- Days to symptom onset- median 11 (0-37) days post-vaccination.
- Symptoms usually suggestive of location of thrombosis:
  - CDC Tier 1 (splanchnic, cerebral venous sinuses)- 23%
  - CDC Tier 2 (venous thromboembolism, pulmonary embolism)- 77%

- Median platelet count at presentation was 76 (7-218).
- PF4 ELISA positive- 53%. Functional assay positive- 74%



Slide acknowledgement: Linny Phuong, CDIC conference June 2022

Public reporting of fatal VITT cases in Australia

- To the 16th June 2022, the Therapeutic Goods Administration (TGA) has identified 13 reports where the cause of death was linked to vaccination from 884 reports received and reviewed
- All deaths linked to vaccination as a likely cause occurred after the first dose of Vaxzevria (AstraZeneca)
- 8 were associated with thrombosis with thrombocytopenia syndrome (TTS) cases
  - CFR overall (8/172)= 4.7%

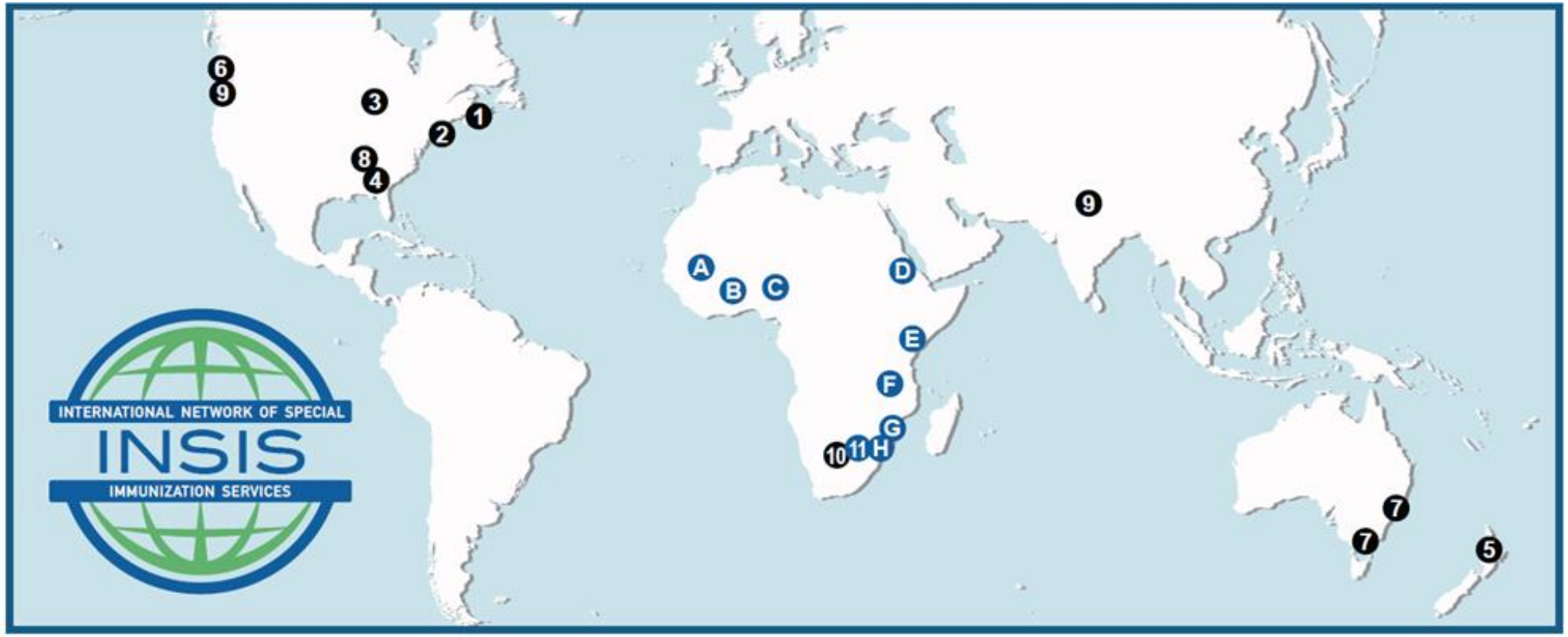
TGA weekly AEFI report

International Network of Special Immunization Services

- The unprecedented scale of the COVID-19 vaccination roll-out presents a unique **opportunity to investigate rare Adverse Events of Special Interest (AESIs).**
- Understanding **mechanisms & risk factors for AESIs** will provide critical information to **advance vaccine safety science**.

- **INSIS** brings together experts in **vaccine safety, specialist clinicians, systems biology, & pharmacogenomics** in several countries **across the globe**.
- Co-Leads: Dr. Karina Top (Canada), Dr. Bob Chen (US).

- ***Aim: To characterize risk factors & mechanisms underlying AESIs following vaccination.***
- Initial targets:
  - **Thrombosis with thrombocytopenia syndrome (TTS)**
  - **Myocarditis, pericarditis**

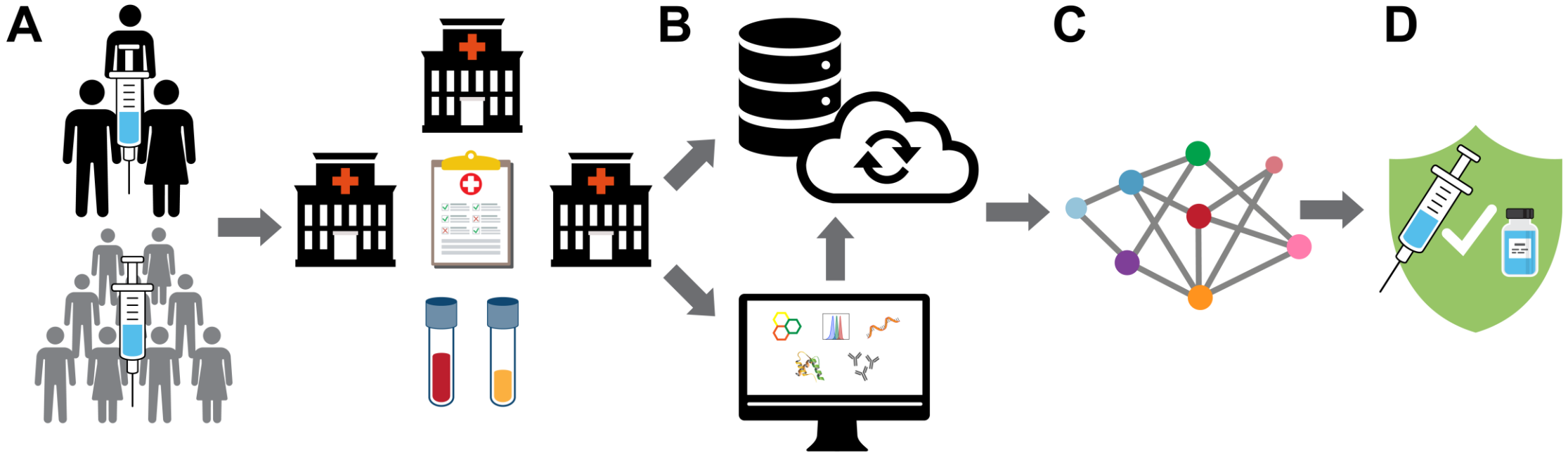


INSIS Participating Sites

1. Special Immunization Clinic Network, Halifax, NS
2. Precision Vaccines Program, Boston Children's Hospital
3. Mayo Vaccine Research Group, Rochester, MN
4. Brighton Collaboration, Decatur, GA
5. Global Vaccine Data Network, Auckland, NZ
6. Canadian Pharmacogenomics Network for Drug Safety, Vancouver, BC
7. AEFI-CAN Network, AUSTRALIA
8. Vanderbilt Vaccine Research Program, Nashville, TN
9. University of Washington, Seattle, Washington (Contact based in New Delhi, India)
10. Vaccines and Infectious Diseases Analytics (VIDA) Research unit (University of the Witwatersrand, Johannesburg, SA)
11. ALIVE Network [African Leadership in Vaccinology Expertise] (Johannesburg, SA)
12. McMaster University, Hamilton, ON
13. Ospedale Pediatric, Bambino Gésu, Rome, IT

Top et al, Clin Infect Dis, 2022; doi: 10.1093/cid/ciac407; Image Credit: Kristin Johnson, *Precision Vaccines Program*, Boston Children's Hospital

INSIS Approach



Case-control design

Harmonized data & sample collection

Samples analyzed using INSIS adversomics pipelines

Clinical & biological data integrated to generate molecular signatures

Top et al, Clin Infect Dis, 2022; doi: 10.1093/cid/ciac407 Image credit: Kristin Johnson, *Precision Vaccines Program*, Boston Children's Hospital

VITT research plans in Australia

Huyen Tran
The Alfred Hospital
Monash University
Melbourne Australia

VITT post dose 2 ChAdOx1 nCoV19 vaccine

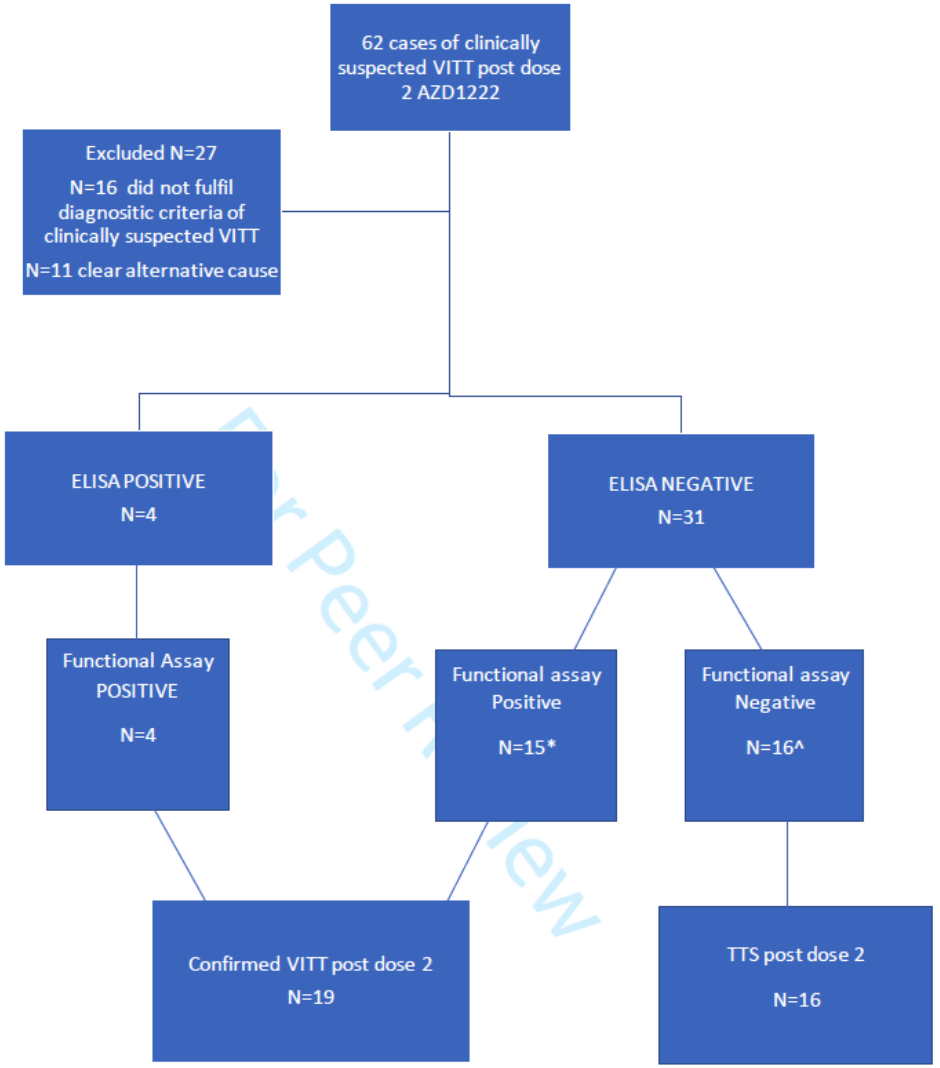


Diagram 1. Clinical suspected VITT samples referred for functional testing.

* Underwent 2nd immunoassay, results were concordant.

^ Underwent functional testing on 2 platforms.

Comparison of VITT after 1st and 2nd dose ChAdOx1 nCoV19 vaccine

Variable	Post 1st dose N= 114	Post 2nd dose N= 19	P value
Age (years) Median (IQR)	61.5 (52, 72)	66 (60,75)	0.18
Time to presentation (days) Median (IQR)	11 (8,16)	13 (9,17)	0.53
Platelet count ($x10^9$/L) Median (IQR)	71 (37, 125)	121 (89, 140)	0.02
D-dimer fold change Median (IQR)	40 (16, 45)	14.5 (10, 24)	0.003
Sex			0.04
Female N (%)	61 (53)	5 (26)	
Male N (%)	53 (47)	14 (74)	
Thrombosis			0.39
Arterial N (%)	14 (12)	4 (21)	
CVST N (%)	25 (22)	1 (5)	
Splanchnic N (%)	14 (12)	1 (5)	
Pulmonary embolus N (%)	38 (33)	8 (42)	
Deep vein thrombosis N (%)	22 (19)	5 (26)	
Mixed arterial venous disease N (%)	12 (11)	3 (16)	
Fatalities	8 (7)	2 (11)	0.59
ELISA			<0.001
Positive N (%)	77 (68)	4 (21)	
Negative N (%)	37 (32)	15 (21)	
Functional assay Positive N (%)	114 (100)	19 (100)	

2 fatal VITT post D2 cases, dosing intervals within 30d of D1

Manuscript in process

VITT cohort study

- Clinical course and outcome over 12m of the Australian VITT cohort

  - Treatment used, outcomes (recovery) and/or complications of treatment (bleeding)
  - Mortality & its predictors
  - Long-term morbidity & predictors of morbidity
  - Physical and psychological impact of VITT diagnosis on patients
  - Safety of revaccination post VITT

VITT Case-control study

Objectives:

- To characterise the clinical risk factors associated with VITT following ChAdOx1 nCoV-19 vaccination.

- Explore potential molecular biomarkers/signatures associated with VITT

Sample size

Cases, N	Controls per case, N	Power
60	600	0.79
65	585	0.81
70	350	0.80

Feasibility
- Cases, >170 VITT
- Controls, local vaccination hubs database access

Sample collection
- Saliva – genomics
- PBMC (limited) – B-cell discovery and antibody screen

80% power at alpha 0.05 to detect an odds ratio of 2.5 given an incidence in the reference population of 0.2

Genomics

- Collaboration with Global Vaccine Data Network

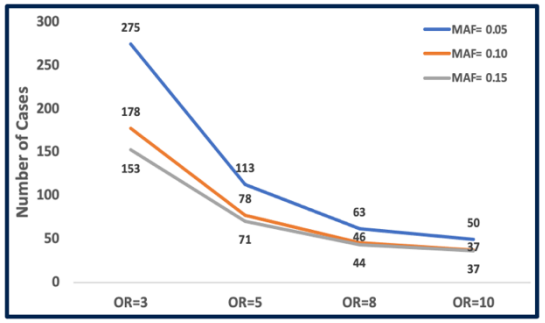


Figure 1. Minimum detectable OR by MAF.

275 cases of VITT needed
2850 AZ controls

- Genome wide association studies
- WES

Global Vaccine Data Network & B Carleton

Multi-Omics

- Transcriptomics (Lynn/Tran)
- Proteomics (Monagle/Tran)
- Lipidomics (McFadyen/Tran)
- Fibrinolysis (Medcalf/Tran)

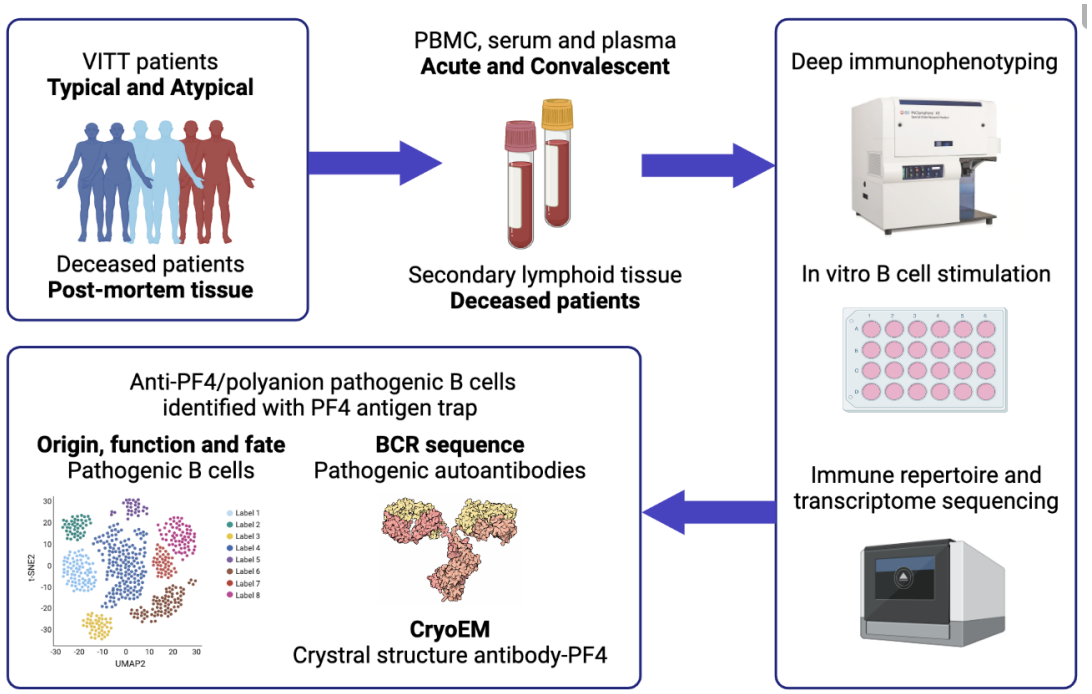
Comparison groups

- ChAd-Ox1 vs Comirnaty - pre and post
- VITT vs ChAd-Ox1 (no AEFI) vs VTE

South Australian Health & Medical Research Institute
Murdoch Children Research Institute
Baker Institute
Australian Centre for blood Diseases

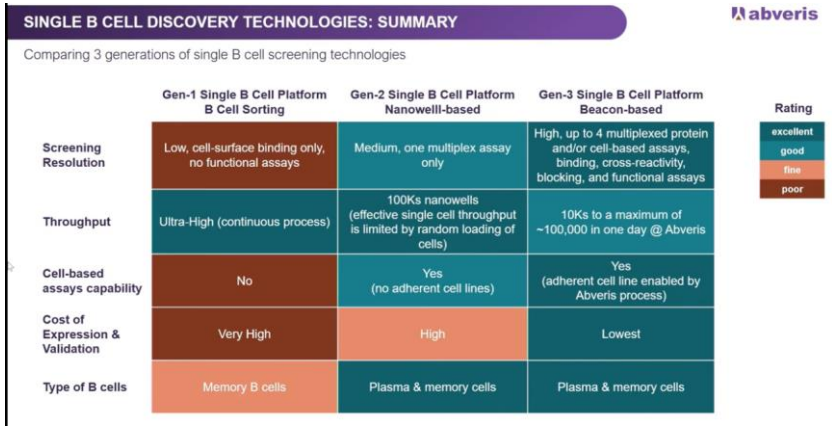
Identification of B-cell clone producing auto-antibody in VITT (1)

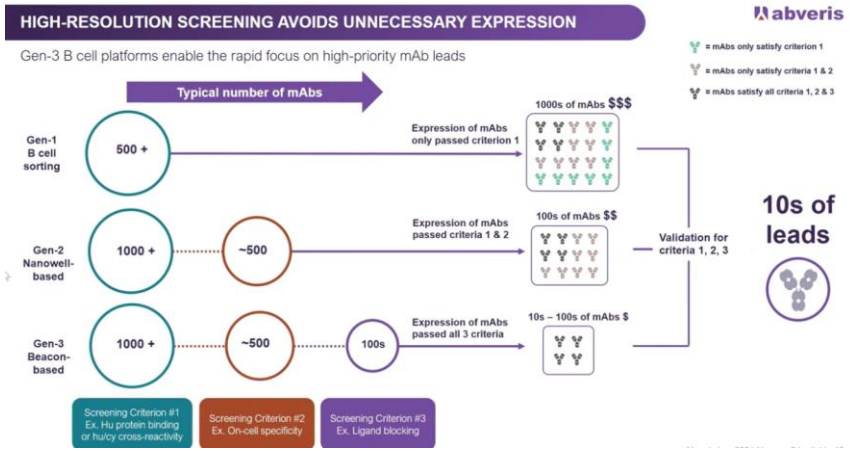
- Simultaneous epitope and transcriptome mapping to sequence the B cell repertoire in the peripheral blood and secondary lymphoid tissues of patients (collected post-mortem) (Phan/Tran).
  - Spatial transcriptomics performed to identify the sites and modes of pathogenic B cell activation & provide the sought-after sequence of pathogenic autoantibodies which will be cloned and expressed



Identification of B-cell clone producing auto-antibody in VITT (2)

- Berkley lights – Beacon Optofluidic system (Whisstock/McFadyen/Tran)
  - Gen 3 Single B-cell discovery
  - PBMC from VITT pts PF4/polyanion
    - Isolate memory B-cells by FACS/MACS
    - Activate and screen against PF4 beads
    - Generate recombinant Fabs & ID structure





Is ChAdOx1 vaccine transduced in megakaryocytes leading to SARS-CoV2 S protein expression within megakaryocytes and their platelet progeny that leads to activating antibody response that drives thrombosis and thrombocytopenia in TTS? (Monagle)

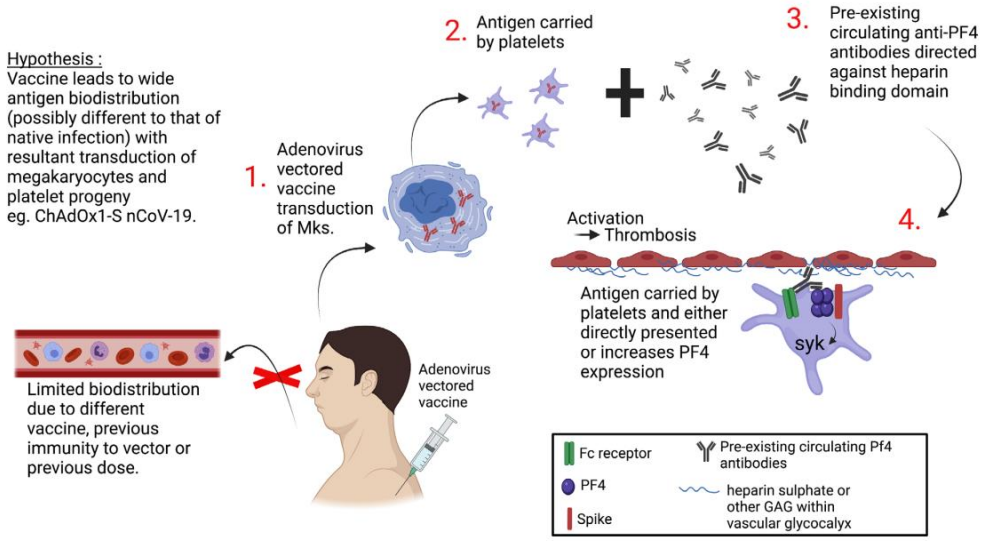


Figure 1. Hypothesis regarding the pathophysiology of thrombosis with thrombocytopenia syndrome (TTS) or vaccine-induced thrombosis and thrombocytopenia (VITT). GAG, glycosaminoglycan; MKs, megakaryocytes; PF4, platelet factor 4; spike, SARS-CoV-2 spike protein with trimeric heparin-binding domains; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; syk, any of the pathways to platelet activation by FcγRIIA including Src, Syk and Btk kinases.

Monagle Immunol Cell Biol. 2021 Nov;99(10):1006-1010. doi: 10.1111/imcb.12505. Epub 2021 Oct 18.

THANK YOU
for your
ATTENTION!

Acknowledgements

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- Research teams that have helped follow-up the cases in Australia
- Funding: Australian Medical Research Future Fund (MRFF)