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Case Definition Companion Guide for Thrombosis with Thrombocytopenia Syndrome (TTS) and Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT)

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DEFINITIONS & ACRONYMS

A/C	Acute / Convalescent
ADAMTS13	A disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13
AESI	Adverse event(s) of special interest
Ag	Antigen
aHIT	Autoimmune heparin-induced thrombocytopenia
AKI	Acute kidney injury
ANA	Antinuclear antibody
ANCA	Antineutrophil cytoplasmic antibody
APS	Antiphospholipid ayndrome
aPTT	activated partial thromboplastin time
AR	Attributable risk
ARF	Acute renal failure
AST	Aspartate aminotransferase
BC	Brighton Collaboration
Bili	Bilirubin
BUN	Blood urea nitrogen
CD	Case Definition
CDC	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness and Innovation
cHIT	Classic heparin-induced thrombocytopenia
CI	Confidence Interval
CM	Clinical Modification (relates to numbered versions of ICD codes)
COPD	Chronic obstructive pulmonary disease
Cr	Creatinine
CVT	Cerebral venous thrombosis
CVST	Cerebral venous sinus thrombosis
CUI	Concept Unique Identifier
DIC	Disseminated intravascular coagulation
dL	Deciliter
DOI	Digital Object Identifier
DVT	Deep venous thrombosis
ELISA	Enzyme-linked immunosorbent assay
GA	Gestational age
Gm/dL	Grams/deciliter
HBV	Hepatitis B virus
HELLP	Hemolysis, elevated liver enzymes, and low platelets (pregnancy complication)
Hgb	Hemoglobin
HIT	Heparin-induced thrombocytopenia

HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HUS	Hemolytic uremic syndrome
iBili	indirect bilirubin
ICD	International Statistical Classification of Diseases and Related Health Problems
INR	International normalized ratio
ITP	Immune thrombocytopenic purpura
IVIG	Intravenous immune globulin
L	Liter
LDH	Lactate dehydrogenase
LLN	Lower limit of normal (for a given reference laboratory)
LMWH	Low molecular weight heparin
LOC	Level of Certainty (as in diagnostic certainty for Brighton CDs)
MAHA	Microangiopathic hemolytic anemia
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (U.K.)
MI	Myocardial infarction
mL	Milliliter
mRNA	messenger ribonucleic acid
Neg	Negative
ng	Nanogram
NOS	Not Otherwise Specified
NS	Not stated
OD	Optical density (relevant to ELISA results)
PE	Pulmonary embolism
PF4	Platelet factor 4
PNH	Paroxysmal nocturnal hemoglobinuria
Pos	Positive
PPSV	Pneumococcal polysaccharide vaccine
PT	Prothrombin time
RI	Relative incidence
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCCS	Self controlled case series
SLE	Systemic lupus erythematosus
SNOMED CT	Systematized Nomenclature of Medicine-Clinical Terms
SPEAC	Safety Platform for Emergency vACcines
SpHIT	Spontaneous heparin-induced thrombocytopenia syndrome
TBili	Total bilirubin
TMA	Thrombotic microangiopathy(ies)
TTP	Thrombotic thrombocytopenic purpura
TTS	Thrombosis Thrombocytopenia Syndrome

UK	United Kingdom
UFH	Unfractionated heparin
ULN	Upper limit of normal (for a given reference laboratory)
URTI	Upper respiratory tract infection
USA	United States of America
UMLS	Unified Medical Language System
USS	Upshaw-Shulman Syndrome (congenital TTP)
VAERS	Vaccine Adverse Event Reporting System
VITT	Vaccine-induced immune thrombocytopenia and thrombosis
VT	Venous thrombosis
VWF	Von Willebrand factor
WG	Working Group (specific to the group that develops BC CDs)

1. Introduction

1. Background

CEPI has contracted with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI prioritized epidemic diseases. Having identified relevant AESI, SPEAC then works to ensure tools and resources are available to facilitate a standard approach to global vaccine safety research and pharmacovigilance activities.

The AESI resources include tabulation of relevant medical codes as well as background incidence data and risk factors. The tools include new case definitions if no published Brighton Collaboration case definition exists, case report forms for standard data collection that would support meeting the case definition levels of certainty and algorithms for assessing level of certainty based on available evidence for each case.

Initially these resources and tools were developed as separate documents but starting in 2021 they were pulled together into a single 'Companion Guide' for each published Brighton Collaboration Case Definition. All Companion Guides are available in the CEPI developer toolbox and on the Brighton website. In addition, since the summer of 2022, all SPEAC Companion Guides are published on the SPEAC community portion of the Zenodo public website (https://zenodo.org/communities/speac_project). This enables all Companion Guides to have a citable DOI.

The focus of this document is to provide a new Companion Guide for the TTS – VITT Case Definition.[1]

2. Objective of this deliverable

To collate SPEAC & BC tools and resources developed for Thrombocytopenia with Thrombosis Syndrome, hereafter referred to as TTS, and Vaccine-induced Immune Thrombocytopenia and Thrombosis, hereafter referred to as VITT.

3. Methods

The methods used are briefly described in Annex 6 along with links to source documents which have more detailed methodology. In addition, any new methodology, relevant to the content of this Guide, is also provided in Annex 6.

4. Results

Outputs are provided in separate appendices, as listed below, to simplify printing as needed.

Annex 1. VITT and TTS Diagnostic Codes for: ICD-9-CM, ICD-10-CM, MedDRA and SNOMEDCT
Annex 2. TTS Background Rates
Annex 3. VITT and TTS Risk Factors

Annex 4. VITT and TTS Case Definition key caveats for diagnosis, data analysis and presentation of safety data as well as guidance on 'real time' investigation of any possible cases that may be identified as part of clinical trials or active surveillance.
Annex 5. VITT and TTS Data Abstraction and Interpretation Form with algorithms for assessing level of certainty and a glossary of relevant terms.
Annex 6. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together many resources and tools related to TTS and VITT, including ICD-9/10-CM, MedDRA and SNOMEDCT codes for data entry or database searching, background rates, risk factors and guidance for real time investigation. It also provides updated tools, which are in the same format as the online versions, for collecting and interpreting clinical data to apply the Brighton TTS and VITT case definitions and determine the level of diagnostic certainty.

SPEAC recommends that the tools be used in order to assign level of certainty for all identified AEFI with features of TTS or VITT

This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

ANNEXES

Annex 1

ICD-9-CM, ICD-10-CM, MedDRA and SNOMED CT Codes for VITT and TTS

1.1 VITT and TTS Diagnostic Codes: ICD-9/10-CM, MedDRA and SNOMED CT[2-6]

VITT and TTS are new conditions and as such, codes for them may appear in future updates of vocabularies that still are actively being updated. Accordingly, we recommend readers to search for new terms that may have come available. MedDRA and SNOMED CT codes became available in December 2021. Prior to this other codes (e.g. HIT) may have been used. The MedDRA Preferred Term of "Thrombosis with thrombocytopenia syndrome" did not exist prior to September 2021 (MedDRA version 24.1). In MEDDRA version 25 this was added. It should be recognized however that broader searches need to be conducted. AstraZeneca used the following search strategy in their first description of the cases: "Thrombocytopenia events were identified from searches for 20 PTs under the high-level term (HLT) of 'Thrombocytopenias' and within the standardised MedDRA query (SMQ) of 'Haematopoietic Thrombocytopenia-Narrow'. Thrombosis events were identified from searches for 383 PTs within the SMQ of 'Embolic and thrombotic events'" (Laffan et al available at https://doi.org/10.1016/j.vaccine.2022.08.007). In large linked datasources, which mostly use ICD10 or SNOMED CT coding, algorithms are used that require thrombocytopenia and thromboembolic events within certain time frames, including 10 (Willame et al available at https://doi.org.10.1016/j.vaccine.2022.11.031; Burn et al available at https://doi.org.10.1002/pds.5419) and 7 days (Shoiabi et al available at https://doi.org.10.1007/s40264-022-01187-y) There are no ICD 9 and there were no ICD-10 codes for vaccine-induced thrombosis or vaccine-induced thrombocytopenia specifically. The ICD10 code for COVID-19 vaccines causing adverse effects in therapeutic use is U12.9, which would include vaccine-induced thrombosis and thrombocytopenia, but also includes other complications as a result of vaccination. In October 2023, the ICD10 code D75.84 became effective (see https://www.icd10data.com/ICD10CM/Codes/D50-D89/D70-D77/D75-/D75.84) .

TABLE 1.1 NARROW SEARCH TERMS FOR VITT

UMLS CUI & Concept Name		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD-9-CM	ICD-10-CM	SNOMEDCT
C5548181	Vaccine-induced prothrombotic immune thrombocytopenia	Vaccine-induced immune thrombotic thrombocytopenia Vaccine-induced prothrombotic immune thrombocytopenia Immune thrombotic thrombocytopenia Prothrombotic immune thrombocytopenia	10087404 10086162 10086161			1156746003
C5578100	VITT	VITT	10087402			
C5674889	Other platelet-activating anti-PF4 disorders	Other platelet-activating anti-PF4 disorders (applicable to: Spontaneous heparin-induced thrombocytopenia; thrombosis with thrombocytopenia syndrome; Vaccine-induced thrombotic thrombocytopenia)			D75.84	

TABLE 1.2 BROAD SEARCH TERMS FOR VITT and TTS. Note: VITT is a specific syndrome that falls under the umbrella of immune-mediated causes of TTS. The table below includes existing terms for TTS without reference to specific causes along with terms for the immune-mediated causes of TTS other than VITT (see Table 1.1)

UMLS CUI & Concept Name		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD-9-CM	ICD-10-CM	SNOMED CT
		Thrombosis with thrombocytopenia syndrome TTS	10086158 10087402 10087403			
		Antiphospholipid syndrome Antiphospholipid antibody with hypercoagulable state			D68.61	
C0019061	Hemolytic-Uremic Syndrome	Hemolytic-uremic syndrome	10019516	283.11	D59.3	
		Hemolytic uremic syndrome	10019515			111407006
		Haemolytic-uraemic syndrome	10018933			
		Haemolytic uraemic syndrome	10018932			
		HUS	10020472			
		Syndrome hemolytic uremic	10042814			
		Syndrome haemolytic uraemic	10060422			
		Hemolytic uremic syndrome of childhood				36568005
		Hemolytic uremic syndrome, adult type				78209002
		Diarrhea-associated hemolytic uremic syndrome				373421000
		Diarrhea-negative hemolytic uremic syndrome				373422007
		Atypical hemolytic uremic syndrome				789660001
C0040034	Thrombocytopenia	Heparin-induced thrombocytopenia (HIT)			D75.82	73397007
		Heparin-induced thrombocytopenia with thrombosis				111588002
		Thrombotic thrombocytopenic purpura				78129009
		Autoimmune thrombotic thrombocytopenic purpura				438476003
		Acquired thrombotic thrombocytopenic purpura				439007008
		Drug-induced thrombotic thrombocytopenic purpura				441322009
C0398650	Immune thrombocytopenic purpura	Immune thrombocytopenic purpura	10074667	287.31	D69.3	
		Idiopathic purpura	10021243			
		Idiopathic thrombocytopenic purpura	10021245			

		ITP	10023095			
		Werlhof's syndrome	10051064			
C0034155	Purpura, Thrombotic thrombocytopenic	Thrombotic thrombocytopenic purpura Thrombocytopenic purpura, thrombotic TTP Purpura thrombopenic thrombotic Purpura thrombopaenic thrombotic Moschcowitz syndrome	10043648 10043562 10050427 10037563 10037562 10073197		M31.1	78129009
C2717961	Thrombotic Microangiopathies	Thrombotic microangiopathy	10043645	446.6	M31.1	126729006 78129009
		Thrombotic microangiopathy NOS	10043646			195360005
		Acute intravascular thrombotic microangiopathy				1144964006
C0200462	Fibrin D Dimer Assay	Fibrin D-dimer	10016577			
C0855429	Fibrin D dimer increased	Fibrin D-dimer increased	10016581			

TABLE 1.3 Broad search terms for THROMBOCYTOPENIA as a criterion in the VITT and TTS case definitions

UMLSConcept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD-9-CM	ICD-10-CM	SNOMED CT
C0040034	Thrombocytopenia	Thrombocytopaenia	10043551			
		Thrombocytopenia	10043554			
		Thrombocytopenias	10043555			
		Thrombocytopenia, unspecified	10043560	287.5	D69.6	
		Thrombopenia	10043569			
		Thrombocytopenic disorder				302215000
		Primary ITP (immune thrombocytopenia)				128091003
		Secondary autoimmune thrombocytopenia				128092005
		Secondary thrombocytopenia				154826009
		Primary thrombocytopenia				267534000
		Immune thrombocytopenia				2897005
		Thrombocytopenic purpura				302873008
		Isolated thrombocytopenia				724637001
		Acquired thrombocytopenia				74576004
C0857305	Thrombocytopenic purpura	Purpura thrombocytopenic	10037561			
		Thrombocytopaenic purpura	10043552			
		Thrombocytopenia purpura	10043558			
		Thrombocytopenic purpura	10043561			
C0242584	Autoimmune thrombocytopenia	Immune thrombocytopenia	10083842			
C0154301	Acquired thrombocytopenia	Secondary thrombocytopenia	10039884	287.4	D69.5	
C0392386	Decreased platelet count	Low platelets	10024922			
		Platelet count decreased	10035528			
		Platelet count low	10035529			
		Platelets decreased	10035545			
		Reduced platelet count	10038213			

		Thrombocyte count decreased	10043546			
		Platelet count below reference range				415116008
C0701157	Primary thrombocytopenia		10036735	287.3		
C0477317	Other primary thrombocytopenia	Other primary thrombocytopenia		287.39	D69.4 D69.49	

Codes for Thrombosis and Thromboembolism: the Companion Guide to Thrombosis and Thromboembolism (LINK) contains codes for the following, which are not repeated here:

- Narrow terms for:
  - Thrombosis and Thromboembolism
  - Pulmonary Thrombosis, Thromboembolism
  - Cerebral thrombosis and cerebral venous sinus thrombosis
  - Stroke in general and for ischemic stroke
  - Myocardial infarction
  - Microangiopathy
  - Pregnancy and post-partum thrombosis and thromboembolism
- Broad search terms for thrombosis and thromboembolism

Annex 2

TTS Background Rates

2.1 Background Rates for Thrombosis with Thrombocytopenia and specific Immune-Mediated possible causes of TTS (not including VITT)[7-30]

TABLE 2.1. BACKGROUND RATES BY GEOGRAPHIC REGION for concurrent thrombocytopenia and thrombosis

Country	Study years	Population (age in years)	Incidence per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
AMERICAs – USA data included in 'Multiple Regions' below					
ASIA – Japanese data included in 'Multiple Regions' below					
AUSTRALIA/OCEANIA – Australian data included in 'Multiple Regions' below					
MIDDLE EAST					
EUROPE					
Multiple countries[8]	**Case ascertainment from electronic databases using codes**				
CVST with thrombocytopenia					
Spain (SIDIAP-H)	2017-2019	26-61	0.1 [0.0-0.2] (6)		
Stroke with thrombocytopenia					
UK (CPRD)	2017-2019	22-59	0.8 [0.6-1.0] (79)		
Germany (IQVIA DA)		32-67	1.9 [1.7-2.1] (369)		
France (IQVIA LPD)		28-65	0.6 [0.4-0.7] (46)		
Netherlands (IPCI)		23-60	0.9 [0.6-1.3] (32)		
Spain (SIDIAP-H)		26-61	4.4 [3.9-5.0] (244)		
Splanchnic vein thrombosis with thrombocytopenia					
UK (CPRD)	2017-2019	22-59	0.1 [0.0-0.1] (5)		
Germany (IQVIA DA)		32-67	0.1 [0.0-0.1] (16)		
Spain (SIDIAP-H)		28-65	0.7 [0.5-0.9] (36)		
Deep vein thrombosis with thrombocytopenia					
UK (CPRD)		22-59	1.3 [1.1-1.6] (127)		

Germany (IQVIA DA)	2017-2019	32-67	1.2 [1.0-1.3] (225)		
Netherlands (IPCI)		23-60	1.0 [0.7-1.4] (34)		
Italy (IQVIA LPD)		37-68	1.5 [1.0-2.0] (39)		
Spain (SIDIAP-H)		26-61	1.0 [0.8-1.3] (57)		

Pulmonary embolism with thrombocytopenia					
UK (CPRD)	2017-2019	22-59	0.9 [0.7-1.1] (84)		
Germany (IQVIA DA)		32-67	1.5 [1.3-1.7] (286)		
France (IQVIA LPD)		28-65	0.5 [0.3-0.6] (39)		
Netherlands (IPCI)		23-60	0.6 [0.4-1.0] (21)		
Italy (IQVIA LPD)		37-68	0.6 [0.4-1.0] (17)		
Spain (SIDIAP-H)		26-61	1.4 [1.1-1.8] (79)		
MULTIPLE REGIONS [9] (USA, UK, Scotland, Netherlands, France, Spain, Germany, Serbia, Australia, Japan; 17 different data sources including administrative health claims, biobank registry, electronic health records, insurance claims data)					
Thrombosis with thrombocytopenia	2017-2019	All ages	1.62 - 150.65		
CVST with thrombocytopenia			0.01 – 0.20		
Hemorrhagic stroke with thrombocytopenia			0.06 – 18.46		
Ischemic stroke with thrombocytopenia			0.05-49.85		
MI with thrombocytopenia			0.39-56.17		
DVT with thrombocytopenia			0.53-34.31		

TABLE 2.2 BACKGROUND RATES BY GEOGRAPHIC REGION for Heparin-induced thrombocytopenia (HIT)

Country [reference]	Study years	Population (age in years)	Incidence per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
AMERICAs – USA data included in 'Multiple Regions' below					
ASIA – Japanese data included in 'Multiple Regions' below					
AUSTRALIA/OCEANIA – Australian data included in 'Multiple Regions' below					
MIDDLE EAST					
EUROPE					
Multiple countries[8]	**Case ascertainment from electronic databases using codes**				
UK (CPRD)	2017-2019	22-59	3.1 [2.8-3.5] (302)		
Germany (IQVIA DA)		32-67	7.8 [7.4-8.2] (1513)		
IQVIA Italy LPD		37-68	6.4 [5.5-7.5] (171)		
France (IQVIA LPD)		28-65	0.2 [0.1-0.4] (20)		
Spain (SIDIAP-H)		26-61	7.2 [6.5-8.0] (396)		

TABLE 2.3. BACKGROUND RATES BY GEOGRAPHIC REGION for Idiopathic Thrombocytopenic Purpura (ITP)

Country reference	Study years	Population (age in years)	Incidence per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA No data					
AMERICAs No data					
ASIA No data					
AUSTRALIA/OCEANIA No data					
MIDDLE EAST No data					
Kuwait[10]	1981-1986	1-14	12.5 (60)*	**NOTE: included both acute (n=41) and chronic (n=19) ITP, distinguished by the time from onset to complete remission: < or > 6 months*	
EUROPE					
Multiple countries[8] **Case ascertainment from electronic databases using codes**					
UK (CPRD)	2017-2019	22-59	7.8 [7.3-8.4] (759)		
Germany (IQVIA DA)		32-67	11.7 [11.2 – 12.		
IPCI		23-60	7.8 [6,9-8.8] (267)		
France (IQVIA LPD)		28-65	2.1 [1.8-2.5] (175)		
Spain (SIDIAP-H)		26-61	16.7 [15.7 – 17/8] (918)		
Denmark[11]	1973-1995	>15	2.68 [2.33-3.03]	2.06 [1.62-2.50]	3.28 [2.74-3/82]
Denmark[12]	1959-1969	≤15	3.19 (433)		
England [13]	1993-1999	≥16	1.6 (245)		
France[14]	2009-2011	<18	2.83 [2.63-3.00]		
		≥18	2.94 [2.84-3.05]		
		All ages	2.92 [2.83-3.01]	2.77 [2.64-2.90]	3.03 [2.90-3.16]
Germany [15]	1996-1997	1.0-1.9		5.84 [4.14-7.55] (45)	3.42 [2.08-4.77] (25)
		2.0-3.9		4.90 [3.38-6.41] (40)	3.49 [2.17-4.81] (27)
		4.0-5.9		3.68 [2.40-4.95] (32)	3.14 [1.94-4.35] (26)
		6.0-7.9		2.58 [1.57-3.59] (25)	2.93 [1.83-4.04] (27)
		8.0-9.9		1.53 [0.76-2.30] (15)	1.08 [0.41-1.75] (10)
		10.0-11.9		0.54 [0.07-1.01] (5)	1.80 [0.92-2.69] (16)
		12.0-13.9		0.87 [0.27-1.47] (8)	0.80 [0.21-1.40] (7)
		14.0-15.9		0.42 [0.01-0.84] (4)	0.89 [0.27-1.51] (8)
		16.0-16.9		0.42 [0.00-1.00] (2)	0.22 [0.00-0.65] (1)
		All ages	2.16 [1.92-2.40] (323)	2.29 [1.95-2.63] (176)	2.02 [1.69-2.34] (147)
Norway [16]	1996-1997	<15	5.3 (92)		

Scandinavia[17]	1998-1999	<14			
Denmark			3.9 (109)		
Finland			5.6 (152)		
Iceland			2.5 (5)		
Norway			5.6 (74)		
Sweden			4.0 (166)		
Turkey [18]	2000-2012	≥16	2.92 [1.57-4.27] (216)	1.5 [0.15-1.85] (159)	4.42 [2.04-6.8] (57
UK [19]	1974-1994	<15	4.8 (70)		
UK [20]	1995-1996	<16	3		
UK [21]	1992-1998	≥18	2.9 [2.5-3.2]	2.1 [1.7-2.6]	3.6 [3-4.2]
	1999-2005		4.5 [4.1-4.8]	3.8 [3.3-4.3]	5.1 [4.6-5.7]
	1992-2005	18-19		0.6	4.9
		20-29		1.6	3.6
		30-39		1.3	3.5
		40-49		1.8	3
		50-59		3	4.2
		60-69		3.9	5.5
		70-79		10.5	6.4
		80-89		9.3	9.2
		90-99		10.3	8.1
		All ages	3.9 [3.6-4.1]	3.2 [2.8-3.5]	4.5 [4.2-4.9]
UK [22]	1990-2005	<18	4.2 [3.7-4.7] (257)	4.7 [3.9-5.5] (148)	3.7 [3.0-4.4] (109)
		18-64	2.9 [2.7-3.2] (534)	2.0 [1.7-2.3] (188)	3.8 [3.4-4.2] (346)
		65-100	7.4 [6.6-8.1] (354)	7.8 [6.6-9.0] (157)	7.1 [6.1-8.0] (197)
		≥18	3.8 [3.6-4.1] (888)	3.1 [2.7-3.4] (345)	4.6 [4.2-5.0] (543)
		All ages	3.9 [3.7-4.1] (1145)	3.4 [3.1-3.7] (493)	4.4 [4.1-4.7] (652)
UK [23]	1990-2005	<18		4.7 [3.9-5.5] (148)	3.7 [3.0-4.4] (109)
		<2		8.7 [5.8-12.6] (28)	4.9 [2.7-8.1] (15)
		2-5		9.7 [7.5-12.6] (69)	4.7 [3.2-6.6] (32)
		6-12		2.6 [1.8-3.7] (33)	3.4 [2.5-4.7] (41)
		13-17		2.1 [1.3-3.3] (18)	2.7 [1.7-4.1] (21)
		≥18		3.1 [2.7-3.4] (345)	4.6 [4.2-5.0] (543)
		18-64		2.0 [1.7-2.3] (188)	3.8 [3.4-4.2] (346)
		≥65		7.8 [6.6-9.0] (157)	7.1 [6.1-8.0] (197)
		All Ages	4.2 [3.7-4.8]		
Europe ACCESS [24] **2017 – 2020 for all participating European countries**					
Denmark – Danish Registry France - SNDS	2017-2020	In- & Out-patients	63.16 [0.00-147.83]		
Italy – ARS	2017-2020	All ages Inpatients and ER	29.55 [26.03-33.08]		

Netherlands - PHARMO	2017-2020	All ages Inpatients	18.01 [16.31-19.70]		
Spain - FISABIO Spain - BIFAP	2017-2020	All ages GP & in-/ outpatients	92.09 [42.47-141.71]		
Italy – Pedianet Spain – BIFAP Spain – SIDIAP UK – CPRD	2017-2020	All ages GP records	38.99 [7.23-70.76]		

MULTIPLE REGIONS					
Americas (US), Asia (Japan), Australia, Europe (France, Germany, Netherlands, Spain) [25]	2017-2019	1-5		17 [12-23]	12 [8-19]
		6-17		8 [3-19]	9 [4-21]
		18-34		8 [2-23]	14 [6-36]
		35-54		10 [3-35]	15 [5-43]
		55-64		19 [6-57]	18 [6-53]
		65-74		30 [9-105]	25 [8-82]
		75-84		41 [10-170]	30 [8-110]
		≥85		56 [15-210]	36 [11-118]

TABLE 2.4 BACKGROUND RATES BY GEOGRAPHIC REGION for Thrombotic Thrombocytopenic Purpura (TTP) only or Thrombotic Microangiopathies (TMA) as a group

Country [reference]	Study years	Population (age in years)	Incidence per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA No data					
AMERICAs					
Oklahoma[26] *Cases found based on requests to Oklahoma blood institute for plasma exchange treatment for TTP or HUS*	1996-2012	All TTP patients: all ages	0.835 [0.802-0.869](333)		
		TTP with ADAMTS13 measured All ages ≥18 years <18 years	0.835 [0.802-0.869](312) 1.319[1.270-1.369](289) 0.309 [0.269-0.350](23)		
		TTP with ADAMTS13 <10% All ages ≥18 years <18 years	0.217 [0.200-0.234](73) 0.235 [0.184-0.300](72) 0.0091[0.0039-0.020](1)	0.102 [0.86-0.119](17)	0.327 [0.297-0.357](56)
ASIA No data					
AUSTRALIA/OCEANIA No data					
MIDDLE EAST No data					
EUROPE					
Germany[27] *ICD10 code to find cases; record review to distinguish first vs recurrent episodes*	2014-2016	Acquired TTP All ages	0.147 [0.128-0.157]		
UK[28] *Confirmed TTP cases admitted to one of 7 teaching hospitals*	2002-2006	Acute TTP 2-78 years	0.6 (178)		
Multiple countries[8] **Case ascertainment from electronic databases using codes**					
UK (CPRD)	2017-2019	TTP; 22-59	0.5 [0.4-0.7] (52)		
Germany (IQVIA DA)		TTP; 32-67	2.8 [2.6 – 3.1] (552)		
Italy		TTP; 37-68	1.7 [1.2-2.3} (45)		

(IQVIA LPD)					
France (IQVIA LPD)		TTP; 28-65	0.6 [0.5-0.8) (52)		
Spain (SIDIAP-H)		26-61	1.5 (1.2-1.9) (82)		
Europe ACCESS [24] 2017 – 2020 for all participating European countries. Event is Thrombotic Microangiopathy					
Denmark – Danish Registry France - SNDS	2017-2020	In- & Out-patients	1.54 [0.34-2.74]		
Italy – ARS	2017-2020	All ages Inpatients and ER	0.62 [0.2-1.03]		
Netherlands - PHARMO	2017-2020	All ages Inpatients	0.47 [0.18-0.76]		
Spain - FISABIO Spain - BIFAP	2017-2020	All ages GP & in-/ outpatients	1.03 [0.75-1.32]		
Italy – Pedianet Spain – BIFAP Spain – SIDIAP UK – CPRD	2017-2020	All ages GP records	0.32 [0.00-0.65]		

TABLE 2.5. BACKGROUND RATES BY GEOGRAPHIC REGION for Antiphospholipid Syndrome (APS)

Country [reference]	Study years	Population (age in years)	Incidence per 100,000 person years [95% confidence interval] (total cases)					
			All		**Males**		**Females**	
AFRICA No Data								
AMERICAs								
USA – Minnesota, Olmsted County[29]	**2000-2015**	18-44	1.6	(13)	1.7	(7)	1.4	(6)
		45-54	1.2	(4)	0.6	(1)	1.8	(3)
		55-64	3.5	(8)	5.4	(6)	1.7	(2)
		65-74	0.7	(1)	0.0	(0)	1.3	(1)
		>75	5.5	(7)	2.0	(1)	7.7	(6)
		All ages	**2.1 [1.4-2.8] (33)**		**2.0 [1.0-3.0] (15)**		**2.1 [1.1-3.1] (18)**	
ASIA No Data								
AUSTRALIA/OCEANIA No Data								
MIDDLE EAST No Data								
EUROPE No Data								

TABLE 2.6. BACKGROUND RATES BY GEOGRAPHIC REGION for Disseminated Intravascular Coagulation (DIC)

Country [reference]	Study years	Population (age in years)	Incidence per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
AMERICAs – USA data also included in 'Multiple Regions' below					
USA, Minnesota – Olmsted County[30]	**2004**	18-39	10 (4)	15 (3)	5 (1)
		40-59	21 (8)	38 (7)	5 (1)
		60-79	64 (10)	95 (7)	36 (3)
		80-99	87 (4)	197 (3)	33 (1)
		All ages	**26 (26)**	**42 (20)**	**12 (6)**
	2005	18-39	5 (2)	5 (1)	5 (1)
		40-59	18 (7)	26 (5)	10 (2)
		60-79	68 (11)	66 (5)	70 (6)
		80-99	85 (4)	63 (1)	96 (3)
		All ages	**24 (24)**	**25 (12)**	**23 (12)**
	2006	18-39	7 (3)	5 (1)	10 (2)
		40-59	26 (10)	41 (8)	10 (2)
		60-79	42 (7)	64 (5)	22 (2)
		80-99	61 (3)	178 (3)	0 (0)
		All ages	**22 (23)**	**34 (17)**	**11 (6)**
	2007	18-39	0 (0)	0 (0)	0 (0)
		40-59	20 (8)	21 (4)	20 (4)
		60-79	68 (12)	134 (11)	11 (1)
		80-99	59 (3)	56 (1)	60 (2)
		All ages	**22 (23)**	**31 (16)**	**13 (7)**
	2008	18-39	12 (5)	14 (3)	9 (2)
		40-59	15 (6)	10 (2)	20 (4)
		60-79	39 (7)	47 (4)	31 (3)
		80-99	95 (5)	54 (1)	117 (4)
		All ages	**22 (23)**	**19 (10)**	**24 (13)**
	2009	18-39	5 (2)	0 (0)	9 (2)
		40-59	13 (5)	10 (2)	15 (3)
		60-79	37 (7)	57 (5)	20 (2)
		80-99	18 (1)	0 (0)	29 (1)
		All ages	**14 (15)**	**12 (7)**	**14 (8)**
	2010	18-39	2 (1)	0 (0)	5 (1)
		40-59	17 (7)	15 (3)	19 (4)
		60-79	41 (8)	43 (4)	38 (4)
		80-99	75 (4)	203 (4)	0 (0)
		All ages	**19 (20)**	**21 (11)**	**16 (9)**

ASIA – Japanese data included in 'Multiple Regions' below					
AUSTRALIA/OCEANIA – Australian data included in 'Multiple Regions' below					
MIDDLE EAST					
EUROPE					
Multiple countries[8]	**Case ascertainment from electronic databases using codes**				
UK (CPRD)	2017-2019	22-59	0.2 [0.1-0.3] (15)		
Germany (IQVIA DA)		32-67	0.4 [0.3-0.5] (79)		
IQVIA Italy LPD		37-68	1.4 [1.0-1.9] (37)		
France (IQVIA LPD)		28-65	0.4 [0.3-0.6] (34)		
Spain (SIDIAP-H)		26-61	3.8 [3.3-4.3] (206)		
Europe ACCESS [24] 2017 – 2020 for all participating European countries.					
Denmark – Danish Registry France - SNDS	2017-2020	In- & Out-patients	5.68 [0.00-11.61]		
Italy – ARS	2017-2020	All ages Inpatients and ER	1.47 [0.69-2.26]		
Netherlands - PHARMO	2017-2020	All ages Inpatients	0.68 [0.32-1.04]		
Spain - FISABIO Spain - BIFAP	2017-2020	All ages GP & in-/ outpatients	2.65 [0.00-5.85]		
Italy – Pedianet Spain – BIFAP Spain – SIDIAP UK – CPRD	2017-2020	All ages GP records	0.11 [0.03-0.20]		
MULTIPLE REGIONS					
Americas (US), Asia (Japan), Australia, Europe (France, Germany, Netherlands, Spain) [25]	2017-2019	1-5		3 [<1-137]	2 [<1-104]
		6-17		2 [<1-44]	2 [<1-48]
		18-34		4 [<1-31]	4 [<1-99]
		35-54		5 [1-56]	5 [<1-75]
		55-64		12 [1-120]	10 [1-89]
		65-74		17 [2-154]	14 [2-97]
		75-84		23 [4-152]	19 [4-94]
		≥85		24 [5-126]	16 [3-89]

Annex 3

Risk Factors for VITT and TTS

3.1 VITT Risk Factors While there are references to TTS in the Table 3.1 evidence, the context is one of TTS following COVID-19 vaccination – i.e., VITT.

TABLE 3.1 VITT RISK FACTORS [1,7, 31-56]

Age	For 170 definite VITT cases identified in the UK the incidence of VITT was higher in patients under 50 years of age (1/50,000 first doses of ChAdOx1 nCoV-19) than in those ≥50 years (1/100,000 first doses)[31] In a UK self-controlled case series[32] the relative incidence(RI) and attributable risk (AR) for CVT after a first dose of ChAdOx1 nCoV-19 vaccine increased as age decreased (also see Table 3.9) • 15-39 years old: RI: 8.7 (95% CI: 5.8-13.0); AR: 16.1 (95% CI 15-17.7) events/million doses • 40-64 years old: RI: 2.2 (1.4-3.2); AR: 3.2 (1.7-4.0) events/million doses ≥65 years old: no increased risk found
Vaccine	COVID-19 adenoviral vector vaccines: significantly increased reporting rates of TTS or VITT as well as several specific thrombotic syndromes such as CVT or CVST have been confirmed for AstraZeneca ChAdOx1-nCOV-19 and for Janssen/Johnson&Johnson Ad26.COV2-S vaccines. (see Table 3.5). It is impossible to compare most individual studies because different case definitionswere used and there were regional variations in case ascertainment. Nevertheless, there was consistency across studies in the trends for significantly increased reporting rates relative to mRNA vaccines or unvaccinated.[33-40] Similarly, the observed incidence of thromboembolic events following ChAdOx1 nCoV-19 vaccine in Norway and Denmark was significantly greater than the expected background incidence based on national linked health data.[41] The standardized morbidity difference was calculated to estimate excess events/100,000 doses of vaccine: • Venous thromboembolism: 10.8 (95% CI 5.6-17.1) excess events/100,000 doses • Cerebral venous thrombosis: 2.5 (0.9-5.2) excess events/100,000 doses • Pulmonary embolism: 3.4 (0.5-7.5) excess events/100,000 doses **Self-controlled Case Series (SCCS) – see Table 3.9** Higgins et al[42] defined TTS as a combination of radiologic confirmed thrombosis with thrombocytopenia that was new in onset and occurred within 5 days following proven thrombus. All clinical data was manually reviewed by hematologists. The only significant vaccine association was among 18-39 year olds during the 4-27 day interval following ChAdOx1 nCoV-19 vaccine. On the other hand, the risk of TTS following within 4-27 days of a SARS-CoV-2 positive test was increased for all ages. Three other studies examined specific thrombotic events but did not confirm that they were concurrent with thrombocytopenia nor did they validate cases against a standard definition.[32, 42-44]

	When focused on thrombotic events only, while most significant associations were for ChAdOx1 nCOV-19 vaccine, there were also some for Pfizer BNT162b2 vaccine. Table 3.9 only lists significant associations found in the SCCS studies. Lack of data on thrombocytopenia and anti-PF4 antibody testing prohibited any conclusions for VITT per se. Case reports of VITT post other COVID-19 vaccines (Sinopharm[45,46] and Sputnik V[47] adenoviral vector vaccines; mRNA vaccines Moderna [48-53] and Pfizer [54-56] as well as a non-COVID-19 vaccine (HPV[57,58]) have been published and reported to pharmacovigilance systems, but causality has not been established. It is possible that these cases represent the background incidence of spontaneous HIT where a triggering infection by Adenovirus or other viral or bacterial agent was not recognized. Further research is needed.

RISK FACTORS FOR OTHER IMMUNE-MEDIATED TTS SYNDROMES

It is beyond the scope of the Companion Guide to provide an exhaustive list of risk factors for each of the immune-mediated TTS syndromes. Patients with ITP have a slightly increased risk of venous thrombosis especially following splenectomy or during treatment with thrombopoietin receptor agonists (TTS-VITT Brighton case definition publication, supplemental material found at: https://www2.cloud.editorialmanager.com/jvac/download.aspx?id=1681751&guid=b1abccc3-ea87-4615-9c01-9568e9a84ac9&scheme=1). Risk factors for Immune Thrombocytopenic Purpura are included in the Companion Guide for Thrombocytopenia (https://zenodo.org/records/6668865) and will not be repeated here. Since preparation of the Thrombocytopenia Guide, there have been multiple reports of secondary ITP as well as recurrence of ITP in those with a prior history of one or more episodes as well as exacerbation of chronic ITP following COVID-19 vaccines.[59-62]

The most frequently recognized risk factors for the other immune-mediated TTS syndromes are presented in Tables 3.2 – 3.4 below, based on expert reviews and specific studies.[59-96]

TABLE 3.2 RISK FACTORS FOR HEPARIN-INDUCED THROMBOCYTOPENIA (HIT, INCLUDING CLASSIC HIT [cHIT] AND AUTOIMMUNE HIT [aHIT] 63-67 and HIT-like syndromes (Spontaneous HIT [SpHIT][68]

Hospital care and surgery	• SpHIT: Knee replacement surgery: estimated risk of 1 case per 300,000 procedures (based on 30 US case reports over a 12 year period and an estimated 750,000 procedures annually). • Reported after incision and drainage of groin cysts
Comorbidity	• SpHIT: Monoclonal gammaopathy[69, 73]
Infection	• SpHIT: Has been reported to occur following a variety of viral (COVID-19, URTI) and bacterial (periodontitis, pneumonia, staphylococcal infection, infected groin cysts) [69] • VITT-like syndrome (clinical picture and anti-PF4 antibody profile very much like VITT, but no prior vaccine exposure): wild type adenovirus infection[70-73]; other infections[73] including RSV, common cold, urinary tract infection
Medication / Toxins	• cHIT and aHIT: Exposure to heparin, including: unfractionated heparin (UFH), low molecular weight heparin (LMWH), heparin flushes, fondaparinux (pentasaccharide anticoagulant chemically related to LMWH) [63] • SpHIT: exposure to non-heparin polyanionic pharmaceutical agents: dextran sulfate, pentosan polysulfate, polysulfated chondroitin sulfate, PI-88 (muparfostat, an anti-oncologic agent)[68]

TTP results from a deficiency or reduced activity of ADAMTS13 which is a von Willebrand factor-cleaving protease (VWF). The pathogenesis involves accumulation in the blood of large platelet-hyperadhesive multimers of VWF which leads to widespread microthrombi in the systemic microcirculation.[74-76] Severe reductions in ADAMTS13 activity can result from a genetic mutation or autoantibody formation. HUS may also be congenital or acquired, with the latter most commonly due to infection with Shiga toxin producing E. coli 0157 H7. Symptomatically there is a lot of overlap between TTP, HUS and other types of acquired TMA and so the risk factors for all are combined in the table below. Where possible specific risk factors for TTP and HUS are identified. Sources of evidence for the overall frequency of causes or risk factors/triggers for TTP and HUS come from national TMA patient registries.[26, 77-82] The largest single registry study was done by Mariotte et al. in France involving 15 years of data from January 1999 to December 2013 and including a total of 772 cases of proven first occurrence of TTP in >18 year olds.[77] The TTP cases represented 24% of all TMA cases. The type of TTP was congenital in 3%; acquired TTP due to autoimmune antibodies to ADAMTS13 in 75% and acquired due to unknown cause (no ADAMTS13 antibodies) in 22%. Overall, 378 (49%) cases were idiopathic and 394 (51%) had identified triggers or known associated conditions. Among all 772 cases the prevalence of identified triggers or known associated conditions was: infection among 118 (15%);(24 HIV related; 94 other bacterial or viral infection); autoimmune disease among 87 (11.3%); cancer among 71 (9.2%); 8.0% pregnancy/puerperium among 62 (8.0%; of note there were 21 cases of congenital TTP that onset during a first pregnancy); transplantation among 27 (3.5%); drug-induced among 11 (1.4%); and other or multiple conditions for 18 (2.3%).

TABLE 3.3 RISK FACTORS FOR Thrombotic Microangiopathies (includes TTP and HUS) [60, 67, 74-76, 84, 85]

Age	Incidence of acquired TTP is 4 times higher in ≥18 year olds versus <18 years; If only considering confirmed TTP cases with <10% ADAMTS13 activity, the incidence in ≥18 year olds is 25 times that in <18 year olds (See Annex 2, Table 2.3)[26]
Sex	Acquired TTP is more frequent in females. Country specific registry data report F:M ratios of: S Korea: 1.36:1[81]; France: 2:1[77]; Australia: 2.8:1[80]; UK: 3:1 [79]
Pregnancy and Puerperium	Pregnancy is an established risk factor or trigger for TTP. In the French registry study[77], 8% of cases were pregnancy associated and of these 1/3 were the first presentation of Upshaw-Schulman syndrome (see Genetics below) occurring in a first pregnancy; 2/3 were acquired TTP.
Genetics	**TTP:** Upshaw-Schulman syndrome (USS) - Inherited gene mutations for ADAMTS13; Usually presents in childhood with a relapsing course but may also have first symptomatic infection during a first pregnancy[77], and has been reported with onset in the 5th and 6th decades in some cases.[82] **HUS:** inherited abnormalities in variety of complement factors[78]
Comorbidity	• **Autoimmune diseases** in particular SLE, but also systemic sclerosis, dermatomyositis, polymyositis, Rheumatoid arthritis, mixed connective tissue disease, Sjogren's syndrome, periarteritis nodosa, ANCA related nephritis, antiphospholipid syndrome and others; • **Cancer** especially gastric, breast and prostate adenocarcinomas • **Bone Marrow and Solid Organ transplant** • **Pancreatitis** • **Cardiac or major vascular surgery** [83]
Infection	• **TTP:** Cases reported in association with HIV[75], COVID-19 infection[85] , influenza, bacterial infections (sepsis, bacteremia, abscess)

	• **HUS:** classic HUS caused by Shiga toxin producing *E. coli* O157 H7 infection
Medication / Toxins [72,74,76]	• Antimicrobial agents (e.g., quinine, trimethoprim, penicillin, rifampin) • Antiplatelet thienopyridine derivatives (e.g., clopidogrel, ticlopidine) • Chemotherapeutic and immunosuppressive agents (e.g., mitomycin C, interferon, gemcitabine, Cyclosporine, tacrolimus)
Vaccine	• Cases have been reported following seasonal and 2009 (H1N1) influenza, rabies and pneumococcal vaccines [84] as well as adenoviral vectored and mRNA COVID-19 vaccines [60,85,] (See table 3.7 below). These represent temporal associations, but as yet there is no proof of causal association.

Antiphospholipid syndrome (APS) is one of the more common causes of acquired hypercoagulability[86, 87], responsible for as much as 20% of unprovoked DVT, 20-30% of strokes in adults aged <50 years and 10-15% of recurrent fetal loss.[88] APS is associated with elevated levels of one or more antiphospholipid antibodies which include lupus anticoagulants, anticardiolipin or anti-2-glycoprotein I antibodies.[86-91] From 1-5% of the general healthy population may have measurable anti-phospholipid antibodies.[86] While the pathogenesis of APS is still incompletely understood it is thought that symptomatic disease is the result of a 'two-hit' process where onset follows exposure to one or more triggering factors in those who already have circulating anti-phospholipid antibodies. Thrombocytopenia is often present in APS due to one or more of: APS antibodies, intravascular Fc receptor-dependent platelet activation, increased thrombin generation and intravascular consumption or concomitant antiplatelet antibodies.[90] Thrombosis is also multifactorial possibly due to APS antibodies inhibiting natural anticoagulant pathways, complement activation, activated cellular components of coagulation or inhibition of fibrinolysis. Further confounding the picture is that anti-PF4 antibodies have been found in some APS patients, however the functional anti-PF4 platelet activation assay will be negative.[91]

TABLE 3.4 RISK FACTORS FOR ANTIPHOSPHOLIPID SYNDROME (APS)

Pregnancy and Puerperium	The association between pregnancy and APS is well known, albeit not well understood. In order to meet the widely accepted APS classification[92] there must be either thrombosis or pregnancy morbidity which is defined as at least one of the following: • ≥1 unexplained death of a morphologically normal fetus at ≥10 weeks GA • ≥1 premature birth of a morphologically normal neonate before 34 weeks GA because of eclampsia, preeclampsia or placental insufficiency • ≥3 consecutive spontaneous pregnancy losses at <10 weeks GA, unexplained by chromosomal abnormalities or by maternal anatomic or hormonal causes
Hospital care and surgery	• Surgical procedures even minor such as biopsies or dental extraction • Major trauma
Comorbidity	• Autoimmune diseases especially SLE in which 10-15% of cases may have APS[86] • Malignancy • Hemodialysis
Infection	• A variety of viral, bacterial, fungal and parasitic infections may trigger APS [93,94]
Medication / Toxins	• Estrogen
Vaccine	• There have been isolated case reports of APS following tetanus toxoid, seasonal influenza and HPV vaccine[95] as well as COVID-19 vaccines [60], but no proof of causality

DIC may accompany VITT, all HIT syndromes and TMAs. As such it is not presented as a separate entity with a table of risk factors. That said a discussion of DIC states is presented by Warkentin[63], who divides them into those that occur in three different settings:

- Prohemorrhagic disorders: Hepatic failure, envenomation, HELLP syndrome, placental abruption, aortic dissection, aortic aneurysm, Kasabach Merritt syndrome, fat embolism, poly- or neuro-trauma, prostate cancer and promyelocytic leukemia.
- Prothrombotic disorders: anti-PF4 disorders (VITT, classic HIT, autoimmune HIT, spontaneous HIT
- Mixed prohemorrhagic and prothrombotic conditions: septic shock, cancer (especially mucin-producing adenocarcinoma), organ destruction (e.g., pancreatitis), severe hemolysis, cardiogenic shock, transplant rejection, idiopathic purpura fulminans.

Table 3.5 Studies examining reporting rate of thrombotic and thromboembolic events after COVID-19 vaccination. Only significant associations are shown in the table.

Author	Country (age group)	Data Source	Vaccine	Vaccine dose	Vaccinees	AESI	AESI Case Definition	Risk Interval post vaccine	End date for reports	Cases	Reporting rate/million doses or persons (95% CI) (unless otherwise specified)
Bikdeli[33]	UK	UK-MHRA	ChAdOx	Not specified	21,200,000	CVST	Not specified	Not specified	14Apr, 2021	77	3.6 (2.7-4.8)
	USA	US-CDC	Ad26		6,850,000				13Apr, 2021	6	0.9 (0.2-2.3)
Schulz[34]	Germany	Web-based questionnaire	ChAdOx	Dose 1	2,320,535	CVT	Codes that fit BC interim CD	0-31 days	14Apr, 2021	27	1.52 (1.00-2.21) per 100,000 person months at risk
McKeigue[35]	Scotland	CT/MRI reports, Medical discharges Death reports	ChAdOx	Not specified	4,032,293	CVT	MD review of image reports to confirm acute primary case	0-28 days	17May 2021	9	3.1 (1.4-5.4)
										7	2.2 (0.9-4.1)
			Pfizer		2,689,488			0-14 days		2	1 (0.1-2.9)
Bhuyan[36]	Europe	AZ global database	ChAdOx	Dose 1	49,230,000	TTS	Brighton interim TTS	0-14 days	30Apr 2021	399	8.1
				Dose 2	5,620,000					13	2.3
See[37]	USA	VAERS	Ad26	Dose 1	14,104,088	TTS	CDC	0-18 days	30Sept2021	54	3.83
			mRNA	Dose 1 / 2	351,007,705					3	0.00855

Boonyawat[38]	Thailand	Thai MOPH	ChAdOx			VITT			31Aug, 2021	5	0.3 (0.1-0.8)
Chan[39]	Norway (<65)	Case series (5) Schultz2021	ChAdOx	Dose 1	133,000	VITT	Not specified	Not specified	15 Apr, 2021	5	3.77 (1.22-8.79)
	Denmark (<65)	Danish Medicines Agency			140,000					2	1.43 (0.17-5.16)
	Netherlands (<65)	Lareb			400,000					8	2.00 (0.86-3.94)
	Italy (<65)	News Report			1,630,000					11	0.67 (0.34-1.21)
	Canada (55-64)	2 case reports			485,000					2	0.41(0.05-1.49)
	Australia (<&≥ 65)	News report			885,000					3	0.34(0.07-0.99)
	France (<&≥ 65)	ANSM national pharmacovigilance			1,430,000					9	0.63(0.29-1.19)
	Spain (<&≥ 65)	News report			2,575,716					12	0.47(0.24-0.81)
	Germany (<&≥ 65)	News report			2,270,000					21	0.93(0.05-0.30)
	UK (<&≥ 65)	MHRA Yellow Card			11,500,000					99	0.14 (0.23-0.84)
	All countries									172	0.73 (0.43, 1.23)

Table 3.6 Self-controlled case series studies examining association between COVID-19 vaccination and TTS, thrombotic, embolic or thrombocytopenic outcomes. Only significant associations are included in the table.

Author	Country	Data Sources	Study period	AESI	Age Group (years)	Risk period	Vaccine	Adjusted Relative Incidence (95% CI)	Attributable Risk per million doses (95%CI)
Higgins[4] [2]	UK	Clinical audit of hospital radiology reports and clinical case notes from 4 English hospitals	01/Jan/21 to 31/Mar/21	TTS defined as radiology- confirmed thrombosis with new onset thrombocytopenia (<150X10^9 /L) concurrent with or within 5 days after thrombus. All clinical data reviewed manually by hematologists	18-39	4-27 days	ChAdOx1	5.67 (1.02-31.38)	Not calculated
					All ages	4-27 days	SARS-CoV-2 Positive test	4.36 (1.95-9.73)	
					40-64			7.92 (2.01-31.26)	
					≥65			3.12 (1.11-8.78)	
Andrews[32]	UK	Vaccine: National Immunisation Management System (NIMS) Hospital admissions: National electronic data (ICD10 code search)	30/Nov/20 to 18/Apr/21	CVT	15-39	4-13 days 14-27days 28+ days	ChAdOx1	16.3 (9.9-27) 6.1 (3.0-12.5) 6.6 (3.5-121.5)	16.1 (15.0-17.7)
					40-64	4-13 days 14-27days		2.7 (1.6-4.6) 2.8 (1.7-4.7)	3.2 (1.7-4.0)
				Other venous thrombosis	15-39	4-13 days 14-27days		2.2 (1.7-3.0) 2.3 (1.8-3.0)	36.3 (28.8-41.8)
					40-64	4-13 days		1.3 (1.1-1.4) 1.3 (1.1-1.4)	16.4 (7.5-24.9)

						14-27days			
				Thrombo-cytopenia	15-39	4-13 days 14-27days		3.7 (2.1-6.4) 3.0 (1.7-5.2)	11.3 (7.3-13.8)
					40-64	4-13 days 14-27days 28+ days		1.9 (1.4-2.8) 2.8 (2.1-3.8) 1.8 (1.3-2.4)	10.1 (7.2-11.9)
								Incidence Rate Ratio (95% CI)	
Hippisley-Cox[43]	England	Vaccine: NIMS for immunisation data; National electronic data for hospital admissions and SARS-COV-2 infection (ICD10 code search)	1/Dec/20 to 24/Apr/21	VTE	≥16	8-14	ChAdOx1	1.10 (1.02-1.18)	
				CVST		8-14	ChAdOx1	4.01 (2.08-7.71)	
						15-21	BNT162b2	3.58 (1.39-9.27)	
				Thrombocytopenia		8-14	ChAdOx1	1.3 (1.19-1.47)	
						22-28		1.26 (1.13-1.42)	
				Arterial thromboembolism		15-21	BNT162b2	1.06 (1.01-1.10)	
				Other rare arterial thromboses		8-14	ChAdOx1	1.21 (1.02-1.43)	
				Ischemic stroke		15-21	BNT162b2	1.12 (1.04-1.20)	
Berild[44]	Norway, Finland, Denmark	National Population Registries; National Patient Registers; National Vaccination Registers	01/Jan/20 to 16/May/21	Coagulation disorders	≥18 (country Variation In terms of age groups offered specific vaccines)	0 to 28	ChAdOx1	2.01 (1.75-2.31)	
							BNT162b2 mRNA-1273	1.12 (1.07-1.19) 1.26)1.07-1.47)	
				Venous thrombosis			ChAdOx1	1.83 (1.56-2.15)	
							BNT162b2 mRNA-1273	1.13 (1.07-1.20) 1.21 (1.02-1.44)	
				Arterial thrombosis			ChAdOx1	2.99 (1.74-5.13)	
							BNt162b2 mRNA-1273	1.24 (1.02-1.50) 2.07 (1.27-3.28)	

				Thrombo-cytopenia			ChAdOx1	4.29(2.96-6.20)	
				Cerebro-vascular disease			ChAdOx1	1.32 (1.16-1.52)	
							BNT162b2	1.09 (1.05-1.13)	
							mRNA-1273	1.21 (1.09-1.35)	

Table 3.7 Case reports of TTP following vaccination as ascertained by literature reviews[60,84,85]

Author Country	Age Sex	Comorbidity	De novo or relapse	Vaccine-Dose	Time to onset (days)	Symptoms + Signs				ADAMTS13		Other laboratory results
							Platelet Count X10^9/L	Hgb Gm/dL	Schisto-cytes	% activity	Anti-ADAMTS13 antibody	
Maayan[96] Israel	40F	None	De novo	Pfizer-2	8	Macroscopic hematuria, fever, somnolence; leg petechiae + ecchymosis	12	9.9	6%	0	51U/ml	NS
	28 M	Obese	De novo	Pfizer-2	28	Dysarthria, chest pain	38	9.1	6%	0	113U/ml	NS
	31F	Prior TTP	Relapse	Pfizer-1	13	Vaginal bleeding, purpura	14	7.7	10%	0	64U/ml	NS
	30 M	Prior TTP	Relapse	Pfizer-2	8	Limb purpura	11	10.8	6%	0	21U/ml	NS
De Brujin [97] Belgium	38F	None noted	De novo	Pfizer-1 Pfizer-2	21 42	Bruising, central serous chorioretinopathy due to micrthrombi in choroid vessels	46	8.9	3%	0	Inhibitor present	⍰ LDH + iBili ⍰ haptoglobin D-dimer 2,600
Guney[98] Turkey	48F	None noted	De novo	Pfizer-1	12	Weakness, nausea, dizziness, bruising; no	88	10.7	present	<0.2%	>90U/mL	⍰LDH

						mention of thrombosis						
Yoshida [99] Japan	57 M	Healthy	De novo	Pfizer-1	7	Fatigue, loss of appetite, jaundice	9	5.5	17.6%	<0.5%	1.9U/mL	↑LDH, Tbili, Cr + BUN, ↓haptoglobin Neg antiPF4
Ruhe [100] Germany	84F	No info	De novo	Pfizer-1	16	Partial hemiplegia, scattered petechiae, severe arterial hypertension; brain mRI- subacute emboli without occlusion	45	7.9	42%	1.6%	82.2U/ml	↑Tbili ARF ↓haptoglobin Neg antiPF4
Giuffrida[101] Italy	83F	Connective tissue disorder steroid induced diabetes	De novo	Pfizer-1	14	Severe anemia, macrohematuria, diffuse petechiae, venipuncture hematomas	23	5.6	10%	<10%	40U/mL	↑LDH + iBili ↓haptoglobin
	30F	Beta thalassemia carrier	De novo	Pfizer-1	18	Diffuse petechiae, intense headache, fatigue	11	8.9	5-10%	<10%	77.6 U/ml	↑LDH + iBili ↓Haptoglobin
Kirpalani[102] Canada	14F	Anxiety, Iron deficiency;	De novo	Pfizer-2	14	Fatigue, confusion,	10	6.3	Occasional	<1%	72U/ml	↑LDH

		postprandial abdominal pain				headache, bruising						⍰Haptoglobin
Innao[103] Italy	33F	Hodgkins Lymphoma Bone Marrow Transplant	De novo	Pfizer-1	9	Marked asthenia, drowsy, purpura, headache, nausea, abdominal pain	1.2	6.8	3%	8%	NS	⍰LDH + TBili ⍰Haptoglobin D-dimer >10,000 Neg antiPF4
Pavenski[104] Canada	84 M	Prior TTP Prostate cancer, hypertension, gout	Relapse	Pfizer-1	7	Lethargy, myalgia, jaundice, anorexia; new atrial fibrillation; brain MRI - new infarct	58	7.2	Few seen	<0.01	NS	⍰LDH, Bili, Cr + troponin ⍰Haptoglobin
Deucher[105] USA	28F	Prior TTP	Relapse	Pfizer-1	6	Arm bruising	57	NS	NS	0	NS	⍰LDH ⍰Haptoglobin
Alislambouli[106] USA	61 M	None noted	De novo	Pfizer-1	5	Confusion, fever, headache, emesis, dark urine, leg ecchymosis; seizure; small subdural hematoma, no thrombus	6	6.5	8%	<3%	NS	⍰LDH D-dimer 2,190
Waqar[107] USA	69 M	Hypertension, 2 prior DVTs,	De novo	Pfizer-2	7d	Severe fatigue, new onset	22	9.3	Present	<2%	>90U/ml	⍰LDH + iBili

		chronic kidney disease; HIV; chronic HBV;				shortness of breath						↓Haptoglobin Prolonged aPTT & PT
Sissa[108] Italy	48F	Relapsing TTP since 2015	Relapse	Pfizer-2	6	Ecchymoses on arms	94	11.5	10%	<3%	88U/ml	↓LDH
Chamarti[109] USA	80 M	Hypertension, Type 2 Diabetes, gout; iron deficient anemia; hyperlipidemia	De novo	Pfizer-2	14	Weakness, malaise; jaundice No thrombus	48	4.8	3+/HPF	<2%	NS	↓LDH, TBili, Cr, BUN + troponin ↓Haptoglobin
Agbariah[110] Switzerland	60 M	Unknown	De novo	Pfizer-1 Pfizer-2	7 10	Ischemic stroke Retrosternal pain + confusion	Severe tcp	Anemic NS	present	<5%	Negative Inhibitor Weakly +	↓troponin Neg antiPF4
Osmanodja[111] Germany	25 M	None noted	De novo	Moderna-1	13	Progressive fatigue, exertional dyspnea, severe headache, dysphasia, petechial rash on legs; no evidence of thrombosis	29	7.4	2.1%	<1%	72.2U/ml	↓LDH + Cr ↓Haptoglobin Neg anti-PF4

Karabulut[112] USA	48 M	Type2 diabetes, prior TTP X 8years, ITP, COVID19	Relapse	Moderna -1	5	Weakness, slurred speech	10	8.8	2-3/HPF	<3%	Elevated Inhibitor	↑LDH ↓Haptoglobin D-dimer 1,450
Francisco[113] USA	57 M		Relapse	Moderna -2	49	Petechial rash	38	12.4	1-3/HPF	<5%	NS	NS
Dykes[114] USA	50F	Congenital TTP diagnosed at age 30 years Otherwise healthy	Relapse	Moderna -2	7	Malaise; impaired coordination; paresthesias; seizure; new left parietal infarcts	98	Normal	2-4/HPF	<5%	Negative	↑LDH Confirmatory genetic mutation Neg anti-PF4
Yocum[115] USA	62F	Hypertension, Gastro-esophageal reflux disease, Hyperthyroid; hyperlipidemia	De novo	ChAdOx-1	37	Altered mental status; scattered petechiae	29	8.2	NS	<12%	NS	↑LDH, AST + troponin Hematuria AKI Neg anti-PF4
Ramanan[116] USA	50F	Type 2 diabetes; hypertension, COPD; cocaine user; bipolar	De novo	Ad26-NS	7	Short of breath; no new thrombosis	11	6.5	Present	<10%	Elevated inhibitor	↑LDH + TBili ↓Haptoglobin D-dimer 9,180

Lee[117] Malaysia	50F	Hypertension – well controlled	De novo	ChAdOx1 -1	12	Dysphasia, acute numbness; petechiae, bruising; no new thrombosis	33	9.9	Present	0%	>94.9 U/mL	⍰LDH + Bili
Al-Ahmad[118] Kuwait	37 M	Heavy smoker, secondary polycythemia	Unknown	ChAdOx1 -1	21	Gradually progressive fatigue, dizziness, headache, short of breath, dark urine, petechiae, jaundiced	14	8.3	14%	2.6%	Positive no value given	⍰LDH + iBili
Wang[119] Taiwan	75 M	No info	Unknown	ChAdOx1 -NS	30	Bleeding(tongue) No new thrombosis	9	10.5	Seen on smear	0.8%	NS	⍰LDH, D-dimer 1,675 Neg anti-PF4
Buetler[120] Switzerland	60 M	Hypertension, stroke 1week after Pfizer-1; hyperlipidemia	De novo	Pfizer-2	10	Confusion, nausea, vomiting No new thrombosis but Thrombotic microangiopathy	25	8.9	35%	<5%	16.7U/mL	⍰LDH + TBili D-dimer 5,543 Neg anti-PF4
Hammami[121] France	55F	Hyperthyroid	De novo	Pfizer-2	10	Fatigue, nausea, diarrhea; petechiae No thrombosis	15	10.7	2%	<5%	90U/ml	⍰LDH + TBili

Kadikoylu[122] Turkey	28 M	Dog bite	De novo	Rabies-3	15	Fatigue, fever, petechiae on legs	15	10.1	Present	0.5%	Not done	↑LDH
Dias[123] England	54 M	Type II diabetes, hypertension, prior MI	De novo	Influenza	5	Agitation, confusion, fever	7	5.7	Present	21%	Antibody present	↑LDH, TBili,BUN, + Cr D-dimer 6258
Ramakrishnan[1][24] USA	60F	Raynaud's and +ANA tests but no proven autoimmunity	De novo	Influenza	4	Fatigue, fever, ecchymoses	96	NS	MAHA on smear	Not done	Not done	↑LDH, BUN + Cr Renal biopsy – fibrin thrombi
Brown[125] England	23F	None noted	De novo	Influenza -NS	14	Spontaneous bruising, pallor	39	9.2	Present	Not done	Not done	↑TBili
Hermann[126] Germany	56 M	Not stated	Not stated	H1N1 flu	13	Not stated in abstract (German article)	22	4.17	24%	67%	Antibody present	↑LDH + TBili ↓Haptoglobin
Kojima[127] Japan	68F	None noted	De novo	PPV23-NS	15	Confusional state, high fever	11	6.8	Present	<0.5%	Inhibitor present	↑LDH + TBili

Annex 4

VITT and TTS Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation

4.1 TTS-VITT Case Definition1 Key Caveats

- TTS implies concurrent presentation of both Thrombocytopenia AND [thrombosis OR impending thrombosis as suggested by a severe and persistent headache that is accompanied by a markedly elevated D-dimer (>4000 nanograms/mL or >8 times the upper limit of normal for the testing laboratory)].
- There are many possible causes of TTS[1]: immune-mediated (see Table 4.1) including VITT, and non-immune-mediated (see Table 4.2).
- When VITT is suspected, the VITT case definition should be used.
- There are two situations when the TTS case definition should be used:
    - When there is a strong suspicion of VITT but insufficient data to meet any VITT CD level of certainty. The TTS CD should be used to enable suspect VITT case classification.
    - When a case meets Level 5 VITT (not a case of VITT) because there is a plausible alternative diagnosis to explain the findings. The TTS case definition can be used to classify cases that could fall under the 'immune-mediated' causes of TTS (see Table 4.1): i.e., TTP or HUS or ALS or ITP with thrombosis. Table 4.1 includes clinical features and diagnostic tests that might help distinguish which entity is more likely, but these are not needed to meet the TTS CD. Note that any of the non-immune mediated TTS conditions (Table 4.2) would be considered plausible exclusions to a case of TTS in this context – i.e., a context which includes a defined interval from vaccination (regardless of specific vaccine) to TTS onset.
- For TTS the interval from vaccination to onset criterion can be dropped in studies that are intended to define background incidence of TTS or in studies comparing vaccine-exposed to non-vaccine-exposed individuals.
- Both VITT and TTS case definitions include an exclusion criterion in situations where there is a more plausible alternative explanation for illness. There are differences between the two CDs in the application of the exclusion criterion and the entities to consider:

  - VITT – there is no exclusion criterion that applies to Level 1 of Diagnostic Certainty because the combination of criteria needed to meet LOC1 are very specific to VITT (i.e., presence of heparin-independent functional platelet activating anti-PF4 antibody as well as D-dimer >4000 ng/mL, thrombocytopenia, confirmed thrombosis or thromboembolism and the typical interval from vaccination to onset). The exclusion criterion does apply to lower levels of diagnostic certainty (2 and 3). Plausible alternative explanations would include all the entities in Tables 4.1 (except VITT) and 4.2.
  - TTS – the exclusion criterion applies to both Levels 1 and 2 of Diagnostic certainty (there is no Level 3). The TTS CD is an umbrella meant to capture all the Immune-mediated causes of TTS (Table 4.1), so none of these are exclusionary. However, all the entities listed in Table 4.2 are plausible alternate explanations that would, if present, indicate a Level 5 of certainty – i.e. not a case of immune-mediated TTS.
- Relative to other case definitions developed when the TTS - VITT signal emerged, the Brighton VITT CD is closest in concept to the UK's Expert Hematology Panel case definition[31] in that neither CD makes any single criterion an absolute requirement. Other guidelines and CDs required thrombocytopenia and there was a great deal of variation in the timing from vaccination to onset[128-137]. The ability to confirm cases that had very high levels of anti-PF4 antibody by ELISA testing as well as presence of platelet activating antibody using functional tests adapted for VITT (as opposed to HIT) enabled a clearer understanding of the variable prevalence of each component criterion in the VITT CD. Specifically:
  - Thrombocytopenia:
    - If multiple tests are done, the lowest platelet count should be used when applying the case definition
    - 5% of VITT cases do not have thrombocytopenia at the time of presentation, although platelet counts drop in most.[31, 138-140]
    - The BC CD for thrombocytopenia uses only the threshold of <150 X 10^9 / L. In contrast the BC VITT CD adds two more criteria, each with equal weight to the <150 X 10^9 threshold. The first acknowledges that in certain populations the lower limit of normal for platelet count is below 150.[141] In such instances, the local reference laboratory Lower Limit of Normal (LLN) can be used instead of 150. The second defines thrombocytopenia as a ≥50% fall from a previously documented count. This recognizes that there are patient populations with a very high baseline platelet count (e.g., counts near the 450 upper limit of normal; post-splenectomy; chronic hematologic disorders such as anemia or myeloproliferative disorders). The WG did not define a timeline for the prior documented count, noting that the higher than usual counts would be stable over time in most of the affected populations.
  - Vaccination to onset interval: with the day of vaccination defined as day 0, three different timelines apply depending on the thrombus location:
    - 4 to 42 days: if there is isolated DVT, PE or both together, there can be a longer timeline to development or recognition.

- 4 to 30 days: applies to all other confirmed thrombus locations (CVT, CVST, splanchnic vein thrombosis, arterial thrombosis including MI or stroke) where the presentation is more explosive.
- 5 to 30 days: applies to the situation where rather than confirmed thrombosis there is severe, persistent headache, which has been termed 'pre-VITT' by some.[142-144] Headache is a very common reactogenicity symptom which is most prevalent during the first few days following vaccination. Accordingly, the WG thought a minimal lower bound of 5 rather than 4 days should be applied to headache.

- Acute or newly diagnosed thrombosis or thromboembolism. There are two possibilities to meet this criterion:
  - Severe persistent headache that onsets from 5 to 30 days after vaccination.[144, 145]
  - Confirmed thrombosis (micro- or macro-vascular) by imaging, surgery or histopathology. The site (typical as in DVT or PE; atypical as in CVT, CVST, splanchnic VT) does not impact on the level of certainty. Some key observations from clinical studies of confirmed VITT cases include:
    - There are often multiple sites in different vascular beds.[31, 40, 138, 146-148] This is particularly true in patients with hepatosplenic thrombosis where 88% had ≥2 sites of thrombosis relative to cases with non-hepatosplenic thrombosis.[149]
    - Hemorrhage often accompanies thrombosis (e.g., intracerebral hemorrhage in CVT; adrenal hemorrhage in adrenal vein thrombosis)[31, 150]
    - Confirmed thrombosis may be asymptomatic.[146, 148, 149, 151] In cases where D-dimer is extremely high or platelets very low consideration should be given to performing total body imaging to identify occult thrombotic sites.[146, 149, 151]
- Elevated D-dimer:
  - If multiple tests are done, the peak value should be used when applying the case definition.
  - In most cases of confirmed VITT, D-dimer is >4000 ng/mL. The VITT CD uses this threshold as the only option for elevated D-dimer. Still there have been confirmed cases where D-dimer is not elevated [139, 151, 152] and the VITT CD enables meeting meet LOC 1, 2 or 3 even with a normal D-dimer. The WG identified a number of situations where the D-dimer isn't elevated: low grade disease, sample for testing obtained after treatment when the clinical illness is improving; patient already on anti-coagulation for other reasons.[1]
- Anti-PF4 antibody: a positive ELISA or functional assay is required to meet level 1 or 2 VITT, but level 3 may be achieved in the absence of a positive anti-PF4 antibody test (would need to meet 3 of the 4 other criteria defined for thrombocytopenia, thrombosis, D-dimer and time-to-onset following vaccination). Some key caveats regarding anti-PF4 testing include:

- Presence of anti-PF4 antibody by ELISA:
  - Commercially available anti-PF4 ELISA kits vary in their sensitivity from 64% to 100%. [153-155] and it is possible to test positive using one assay and negative using another. As such, when VITT is suspected but the ELISA test is negative, it is recommended to retest using a different assay if possible.
  - There is a correlation between the magnitude of the optical density (OD) reading in a positive ELISA assay and the likelihood that the functional assay for platelet activating anti-PF4 antibody will be positive [153, 156] Specifically, Schönborn *et al.* tested over 900 samples by both ELISA and functional assays[156] and found
    - 672 ELISA negative samples (OD<0.5): 0% positive by functional assay
    - 72 ELISA weak positive (OD from 0.5-<1.0): 4.2% positive by functional assay
    - 32 ELISA moderately positive (OD from 1.0-<1.5): 21.9% positive by functional assay
    - 18 ELISA strongly positive (OD from 1.5-<2.0): 50% positive by functional assay
    - 160 ELISA very strongly positive (OD ≥2.0): 97.5% positive by functional assay.
  - In longitudinal studies of confirmed cases of VITT it has been shown that ELISA positivity can persist for several months[157-161]. Provided blood samples are available, it may be possible to retrospectively confirm a suspect case as true VITT by retrospectively testing for anti-PF4 by ELISA up to 20 weeks following presentation[160].
  - ELISA may detect anti-PF4 antibodies in 5-8% of healthy blood donors[162], patients with periodontal disease[163] or after COVID-19 vaccination in asymptomatic individuals.[164-168] In such settings the OD level is usually low albeit above the threshold for test positivity. These antibodies are non-pathogenic and thus a functional test for platelet activating antibodies will be negative and can help to rule out VITT. (See Table 3.3)
  - Rapid assays (chemiluminescence immunoassays, lateral flow assays, particle gel immunoassays) that were developed for HIT diagnosis are negative in VITT and should not be used.[169, 170]
- Presence of functional platelet activating anti-PF4 antibody:
  - Rarely, the functional assay may be negative in confirmed VITT. There are a few possible reasons:
    - Extremely high anti-PF4 antibody titer (ELISA OD >1.0) may hinder formation of large antibody-platelet complexes which is necessary for test positivity: in such cases a 1/5 or 1/10 dilution of the serum will result in a true positive test [156]
    - Patient received high-dose IVIG treatment prior to sampling for a functional assay.

Table 4.1 Key Diagnostic Features for Immune-mediated Causes of TTS (based on supplemental material published with the TTS-VITT Brighton case definition1) Disseminated intravascular coagulation (DIC) may be seen in many if not all of the entities in the table below and presence or absence of DIC is not a distinguishing feature.

Immune-Mediated	Features, Pathogenesis, Diagnostics
VITT	**Suspect:** thrombocytopenia with confirmed thrombosis/severe headache with D-dimer >4000 ng/uL that onsets from 4/5 to 30 days (or up to 42 days if isolated DVT or PE) after vaccination **Thrombocytopenia:** Usually but not always present, especially early in the course of illness. Usually not <20X10^9 /L **Thrombosis:** Typical (DVT, PE) and atypical (CVST, CVT, splanchnic veins) sites involved and often multiple sites, some of which may be occult/asymptomatic. **D-dimer:** Typically very elevated, >4000 ng/mL or >8 times reference laboratory upper limit of normal. **Diagnosis:** First line test would be ELISA for anti-PF4 antibody testing. An OD >2.0 is highly predictive of a positive functional assay for pathological platelet activating anti-PF4 antibodies.[156] In such situations the functional assay need not be done. It is possible to have falsely negative ELISA tests[153-155], and in cases where there is strong suspicion for VITT, a repeat ELISA by a different test kit should be considered. In confirmed VITT the ELISA assay may remain positive for several months so it may be possible to make a diagnosis retrospectively if blood samples are available. The functional assay may help to confirm cases where the ELISA is not strongly positive.
VITT-like syndrome	**Suspect:** similar presentation to VITT, with anti-PF4 antibodies but no vaccine exposure. Known triggers include wild-type adenovirus infection, other respiratory tract infections including RSV.
Antiphospholipid antibody syndrome (APS)	**Suspect:** can overlap with other TTS syndromes but a unique feature may be recurrent fetal loss **Thrombocytopenia:** present in 20-30% of APS[59,85]; typically mild and intermittent **Thrombosis:** may present in typical (DVT, PE) or atypical (CVST, splanchnic veins) sites or involve microvasculature sometimes with digital ulceration, gangrene and livedo reticularis. **Diagnosis:** The consensus classification for APS[91] requires: • ≥1 of the following clinical conditions: ○ Proven (imaging or histopathology) venous, arterial, small vessel or microvasculature thrombosis

	○ Pregnancy morbidity as indicated by ≥1 of the following: ▪ ≥1 unexplained death of a morphologically normal fetus at ≥10wks GA ▪ ≥1 premature (before 34 weeks GA) birth of a morphologically normal neonate because of eclampsia, preeclampsia or placental insufficiency ▪ ≥3 consecutive spontaneous pregnancy loses at <10weeks GA, unexplained by chromosomal abnormalities or by maternal anatomic or hormonal causes AND • ≥1 anti-phospholipid antibody listed below when measured on at least 2 occasions ≥12 weeks apart ○ Lupus anticoagulant ○ Anti-cardiolipin ○ Anti-beta2 Glycoprotein
Thrombotic thrombocytopenic purpura (TTP)	**Suspect**: when there is Microangiopathic hemolytic anemia – 'MAHA': (Hgb <12g/dL, Coombs test negative, ↑ reticulocyte count, ↓ serum haptoglobin <10mg/dL, presence of 2 or more schistocytes/high power field on peripheral smear, ↑LDH / total or indirect bilirubin). Usually normal PT, aPTT, INR. **Thrombocytopenia**: typically present and often moderate to severe with platelets <30,000 X 10^9 /L **Thrombosis:** involving microvasculature which can present as organ ischemia especially brain, heart, mesenteric vasculature **Specific Diagnosis:** TTP is considered confirmed if there is a measured severe decrease in ADAMTS13 activity – usually defined as <10%. In **acquired autoimmune TTP** (majority of cases) autoantibodies to or inhibitors of ADAMTS13 will be measurable. In **congenital TTP** (3-5% of all cases based on national registries[75-77] activity is very low but anti-ADAMTS13 antibodies are not detected. In such cases gene sequencing may confirm the presence of the ADAMTS13 gene mutation. Of note the congenital form can present for the first time later in life, particularly during a first pregnancy. **Acquired TTP of unknown cause** (20% or more of cases): Substantial clinical overlap between TTP, HUS and other thrombotic microangiopathies (TMA) along with variable ADAMTS13 activity and presence or absence of ADAMTS13 antibodies/inhibitors can make diagnosis very difficult.

Hemolytic Uremic Syndrome (HUS)	**Suspect:** MAHA profile (see TTP above) that onsets after an acute hemorrhagic diarrheal illness. Renal involvement due to microangiopathic thrombosis is a prominent feature with elevated BUN, creatinine and may be acute renal failure. **Thrombocytopenia:** similar to TTP **Thrombosis:** similar to TTP but renal thrombotic signs and symptoms more prominent **Diagnosis:** Isolation of Shiga toxin producing *E. coli O*157 H7 or O104 H4; not definitive but ADAMTS13 activity less likely to be severely reduced and anti-ADAMTS13 antibodies usually negative or weak positive
Heparin induced thrombocytopenia (HIT)	The following refers to what is considered 'classic' HIT. There are rarer versions with different triggers, patterns of disease onset or response to stopping heparin (Autoimmune HIT[63], Spontaneous HIT[68]). Also see Annex 3, Table 3.2 **Suspect:** Onset is 5-10 days after prophylactic or therapeutic administration of heparin to surgical patients. **Thrombocytopenia:** typically present but mild to moderate and usually rapid recovery in platelet counts occurs after stopping heparin (median of 4 days). **Thrombosis:** venous thrombosis much more prevalent than arterial thrombosis; CVST or CVT uncommon (<5% of cases) **Diagnosis:** Assays for heparin-dependent anti-PF4 antibodies, including ELISA, rapid assays (such as: chemiluminescence immunoassay, latex immunoturbidimetric assay, lateral flow immunoassay, particle gel assay) and functional platelet activation assays are positive.[63,68,170]
Immune thrombocytopenia (ITP) where there is also thrombosis	**Suspect:** typical presentation is acute onset of spontaneous bleeding, especially in skin or mucosal with associated thrombocytopenia. **Thrombocytopenia:** typically severe with platelet count <20 X 10^9 /L **Thrombosis:** relatively infrequent but may complicate the course in the context of splenectomy or therapy with thrombopoietin receptor agonists. **Diagnosis:** ITP No specific test however antiplatelet auto-antibodies are found in up to 60% of cases [61]

Table 4.2 Non-immune-mediated causes of TTS[1, 64] In some cases the same process leads to both thrombosis and thrombocytopenia, whereas in others there may be separate causes for thrombosis and thrombocytopenia, even though they present concurrently.

Cancer-associated thrombosis & thrombocytopenia • Most commonly seen with adenocarcinoma, especially mucin-producing tumors. Most common thrombosis is DVT. The tumor may trigger uncontrolled thrombin generation resulting in intravascular platelet activation and thrombocytopenia.
Trauma-associated thrombosis & thrombocytopenia
Diabetic ketoacidosis • Thromboembolic complications including CVST may be seen. Pathogenesis not clear but may be due to hyperaggregable platelets in settings of high glucose levels or activation of the coagulation cascade.[171]
Thrombosis in patients with hypo-proliferative thrombocytopenia due to cancer
Thrombosis in patients with liver disease and thrombocytopenia secondary to liver disease
Thrombosis in patients with thrombocytopenia due to alcohol abuse
Stroke or peripheral artery embolism in patients with atrial fibrillation and low platelet counts due to other reasons (e.g., liver disease)
Septicemia with thrombosis (e.g., aortic valve endocarditis; sepsis-induced DIC, especially in meningococcemia) • Sepsis leads to increased thrombin generation plus depletion of anticoagulant factors (protein C, protein S, antithrombin) leading to dysregulated fibrin deposition in the microvasculature.[172, 173] • There may be associated DIC as well as septic emboli.
Severe pulmonary embolism with thrombocytopenia • Mild to moderate thrombocytopenia is often seen in association with pulmonary embolism. If there is associated DIC the thrombocytopenia can be severe. Causes of thrombocytopenia could be thrombin-induced platelet activation or platelet consumption with the thromboemboli.[174]
HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) Syndrome
Thrombosis in a pregnant woman with benign pregnancy-related thrombocytopenia
Congenital TTP
Atypical HUS due to complement regulation defects
Thrombosis in a patient with hypo-proliferative thrombocytopenia due to Vitamin B deficiency or toxic drug effects (e.g., valproate treatment)

Thrombosis in a patient with hereditary thrombocytopenia
Paroxysmal nocturnal hemoglobinuria (PNH) • Acquired prothrombotic disorder due to clonal expansion of stem cells which have lost ability to express glycosylphosphatidylinositol-anchored proteins on their cell membranes. Some of these proteins regulate complement and protect cell surfaces. In their absence there is increased complement-mediated hemolysis of red cells which may be associated with TTS. In patients with known PNH, acute infection or vaccination may trigger increased complement activation, exacerbating hemolysis and thrombosis. [175]
Cerebral malaria

Table 4.3 Prevalence of anti-PF4 ELISA and platelet activating antibodies (positive functional assay) in non-VITT situations

Author (country)	Anti-PF4 ELISA assay	Subjects	Sampling timeframe Median(range) in days	antiPF4 Ab prevalence (95%CI)	Anti-PF4 ELISA OD>1	Positive Functional Assay
Noikongdee[166] (Thailand)	Hyphen Biomed Zymutest IgG (+ if OD >0.3)	221 ChAdOx vaccinees	23 (18-27) days	2.3% (0.7-5.2)	0	0
		232 CornaVac vaccinees	18.5 (10-34) days	1.7% (0.5-4.4)	0	0
		193 unimmunized controls	NA	0	0	0
Uaprasert[167] (Thailand)	Hyphen Biomed Zymutest IgG (+ if OD >0.25)	521 ChAdOx vaccinees	5-30 days post dose 1	3.1% (1.8-4.9)	2(both <2)	0
		146 unvaccinated controls	NA	4.1% (1.5-8.7%)	0	0
Barefah[168] (Saudi Arabia)	Asserachrom HPIA IgG (Stago)	94 ChAdOx1 or Pfizer vaccinees	14-21 days after dose 1	5.3% (4/5 had anti-PF4 Ab pre-vaccine)	0	ND
Sorvoll[165] (Norway)	LIFECODES PF4 IgG (Immucor) (+ if OD ≥0.4)	492 ChAdOx1 vaccinees	10-35 days after dose 1	1.2% (0.4-2.2%) (6+)	2 (highest 1.16)	0
		110 blood donors	NA	0		
Hursting[164] (USA)	GT1 ELISA (+ if OD >0.4)	3795 blood donor units	NA	4.3% (3.7-5.0%)	11(highest 1.99)	Not done

4.2 Recommendations for real time assessment

Given the life-threatening nature of VITT and other TTS, it is beyond the scope of the Companion Guide to recommend real time assessment. There are several excellent overviews of TTS and VITT that provide guidelines for investigation and management of VITT and other immune-mediated TTS syndromes[63-65], including in settings where resources may be limited.[176]

In the setting of large phase III or postmarket clinical vaccine trials, especially if involving adenoviral vector vaccines, there should be plans in place for rapid assessment, investigation and management of any suspect VITT or other immune-mediated TTS syndromes (APS, TTP, HUS, SpHIT). If there are no local hematologic or transfusion medicine experts it should be possible to identify expert help available from a distance, for telemedicine consultation and guidance re investigation. While specialized anti-PF4 antibody testing may not be available locally, efforts should be made to identify regional centers where confirmatory testing can be done. Also, blood samples should be taken prior to IVIG therapy which can interfere with functional anti-PF4 antibody tests. Finally, it may be possible to retrospectively diagnose VITT cases months after the acute illness because of the known persistence of ELISA anti-PF4 antibodies.

In settings where case ascertainment is done by searching administrative health data for relevant ICD10, SNOMEDCT or other codes it should be noted that in at least one study set in Scotland, ICD10 codes had a low sensitivity for finding CVT and case ascertainment was higher using expert review of CT scan and MRI reports.[177]

4.3 Data Collection Guidelines

Thrombocytopenia

- If there are multiple platelet counts, the lowest platelet count during the course of illness should be specified
- Specify which criterion was met for thrombocytopenia
    - Absolute platelet count <150 X 10^9/L
    - ≥50% drop in platelet count from a known baseline count. Note that a timing for baseline count is not specified. The Working Group subject matter experts agreed that for conditions where platelet count is at the high end of the normal range, or higher than normal because of an underlying condition, the values are usually stable over time. That said the timing of the baseline count should be specified.
    - A count that is below the lower limit of normal for a local reference laboratory, but the lower limit of normal is <150 X 10^9/L. In this case the reference lab range of normal should be used.

D-dimer

- If reporting the value of D-dimer as a multiple of the local reference laboratory upper limit of normal (ULN), the local ULN value should be specified
- If there are multiple D-dimer measurements, the peak value during the illness should be used

Interval from vaccination to onset of illness

- The day of vaccination should be defined as day 0
- When there are multiple cases the proportion of cases falling into each of the following intervals should be specified:
    - 0 to <4 days after vaccination
    - 4 to 14 days after vaccination
    - 15 to 30 days after vaccination
    - 31 to 42 days after vaccination
    - >42 days after vaccination

Alternative diagnoses for clinical illness

- Where possible, but especially in vaccine research settings, investigation for alternative diagnoses should be conducted and documented for any cases that are excluded as a result (Level 5 of diagnostic certainty).
- In all settings, history and physical exam findings that may pertain to an alternative diagnosis should be noted (e.g., history of cancer, atrial fibrillation, liver disease, alcohol abuse, recent trauma, or pregnancy. For a full list see Tables 4.1 (applies to VITT) and 4.2 (applies to both VITT and TTS). Similarly, any investigations that may have been done to rule out alternative causes should be documented if known.

4.4 Data Analysis Guidelines

- VITT: classify reported events in one of five categories:
  - Meets case definition at:
    - Level 1 of diagnostic certainty (definite case)
    - Level 2 of diagnostic certainty (probable case)
    - Level 3 of diagnostic certainty (possible case)
  - Fails to meet case definition because:
    - Level 4: insufficient information available to meet Level 1, 2 or 3
    - Level 5: An alternative diagnosis for the clinical illness found (applies only to VITT Levels 2 and 3 of certainty).

  →NOTE: cases that meet VITT Level 4 or 5 should be assessed against the TTS case definition.
- TTS: classify reported events in one of four categories:
  - Meets case definition at:
    - Level 1 of diagnostic certainty (definite case)
    - Level 2 of diagnostic certainty (probable case)
  - Fails to meet case definition because:
    - Level 4: insufficient information available to meet Level 1 or 2
    - Level 5: An alternative diagnosis for the clinical illness found (applies to both Levels 1 and 2 of certainty).

Annex 5

VITT and TTS Data Abstraction and Interpretation Forms With Algorithms for Assessing Level of Certainty And Glossary of Terms

5.1 VITT and TTS Data abstraction and interpretation form with algorithms for assessing level of certainty.

The form is organized in a series of Steps presented as tables.

- Step 1 guides the collection of data needed to meet the case definition criteria for both TTS and VITT. Depending on the specific criterion, data are collected using two formats:
    - i. as mutually exclusive answers of YES, NO or UNKNOWN to a series of questions
    - ii as a checklist of specific things that were noted to be present (i.e. YES) like signs or symptoms, or lab test results.

  Relatively simple criteria used in the case definition may be defined directly in step 1. Others may require formulae to define – as done in Step 2.
- Step 2 uses some or all data entered in Step 1 to assign values (YES, NO or. UNKNOWN) to each case definition criterion.
- Step 3 is a small tabular summary of the assigned value (YES, NO or UNKNOWN) for each criterion in the case definition.
- Step 4 provides a tabular algorithm to assign the Level of certainty that meets the case definition (Level 1, 2 or 3) or that does not meet the case definition (Levels 4 and 5).
- A Pictorial algorithm is presented that presents all the relevant criteria needed to meet the case definition and a flow diagram that shows the path to each level of diagnostic certainty depending on the criterion values.
- A Glossary of Terms is also included.

The abstraction form can be used in several settings:

- As a case report form for data abstraction from a hospital/other institutional chart as part of epidemiologic studies of background incidence or to test for causal association between vaccine (s) and TTS or VITT
- Guide data collection for case validation (all or a subset) in studies where electronic health data were used for case ascertainment based on selected medical codes (ICD9/10, SNOMEDCT, MedDRA) or laboratory/radiologic results
- Serve as a supplement to a prospective clinical trial case report form where one or more cases of TTS or VITT may be observed during the course of the trial. In such settings it may also serve as a guide for the type of data to be collected and investigations to be done at the time a possible case is identified.
- Supplement national pharmacovigilance AEFI report forms in case of the occurrence of a safety signal related to TTS or VITT
- Help to organize the data available in an Adverse Event Following Immunization Report form relative to what is needed to assign a level of certainty. Equally important the form will make it clear what data are missing and help to guide case follow-up when feasible.

The data form will also be available online as part of an Automated Brighton Classification (ABC) tool.

TABLE 5.1 <AESI> KEY CASE DEFINITION CRITERIA AND LIKELY SOURCES OF RELEVANT INFORMATION. Space is also provided to record the actual sources of information.

Criterion	Criterion category	Likely sources of information	Actual sources of Information
A	Thrombocytopenia	• Laboratory results – CBC, peripheral smear; D-dimer measurement	
B	Elevated D-dimer		
C1	Confirmed Thrombosis or Thromboembolism – acute or new onset	• Autopsy or Biopsy report • Surgical report • Radiologic Imaging results (includes compression ultrasonography, contrast catheter venography, magnetic resonance (MR) or Computed Tomography (CT) venography, angiography, venography, abdominal ultrasound, CT or MRI scans	
C2	Severe persistent headache with onset from 5-30 days after vaccination	• Clinical notes for illness history in outpatient, emergency or hospital setting • Same as for D	
D	Characteristic Interval from vaccination to onset	• Immunization date by history or vaccination card or enrolment in vaccine trial • Symptom onset in same sources as listed for C above	
E	Anti-PF4 Antibody	• Laboratory results – may be specialized laboratory test that has to be sent to a reference lab – but this should be noted in the clinical records – as outlined in C above	
F	Clinical evidence for presence of thrombosis or thromboembolism (includes physician diagnosis of thrombosis or thromboembolism síndrome or documentation of clinical signs and symptoms typically seen in thrombosis or thromboembolism)	• Outpatient clinic / emergency room record(s) • Hospital: admitting diagnosis; admitting history & physical exam; ICU admission and followup notes; discharge summary; discharge diagnosis • Hematology consultation / other consultations including neurology (in case of stroke or cerebral venous or venous sinus thrombosis), Gastroenterology (in case of	

		abdominal thromboses), Pulmonary (in case of pulmonary embolism)	
X	More plausible alternative diagnosis to explain the clinical illness	• Admission diagnosis; history and physical examination including assessment of differential diagnosis • Hospital discharge diagnosis; discharge summary • Subspecialty consultation notes or clinic records	

Step 1 Complete all rows in the case data entry form that provide an answer option

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was absent or not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent OR nothing was documented about the criterion

Terms with a glossary definition

Criterion	Question	Possible Answers		
A – Thrombocytopenia				
A1	Platelet count < 150 X 10^9 /liter	☐ YES	☐ NO	☐ UNKNOWN
A2	Platelet count below the local laboratory lower limit for a normal count	☐ YES	☐ NO	☐ UNKNOWN
A3	Platelet count shows a ≥50% decrease from a previously documented count	☐ YES	☐ NO	☐ UNKNOWN
B– Elevated D-dimer				
B0.1	Was D-dimer measured? *If YES, answer B0.2 below*	☐ YES	☐ NO	☐ UNKNOWN
B0.2	Was D-dimer within the range of normal for age? *If NO, answer B1, B2, B3 and B4 below based on the peak D-dimer level measured during the clinical illness.*	☐ YES	☐ NO	☐ UNKNOWN
B1	Peak D-dimer above upper limit of normal for age but <2 times upper limit of normal	☐ YES	☐ NO	☐ UNKNOWN
B2	Peak D-dimer elevated from 2 to <4 times upper limit of normal for age	☐ YES	☐ NO	☐ UNKNOWN
B3	Peak D-dimer elevated from 4 to ≤ 8 times upper limit of normal for age	☐ YES	☐ NO	☐ UNKNOWN
B4	Peak D-dimer elevated >8 times upper limit of normal for age (corresponding to >4000 ng/mL)	☐ YES	☐ NO	☐ UNKNOWN
C – Confirmed Thrombosis or Thromboembolism or Pre-VITT				
C0.1	Was thrombosis or thromboembolism confirmed by ≥1 radiologic imaging study? *If YES, specify location(s) in C*	☐ YES	☐ NO	☐ UNKNOWN
C0.2	Was thrombosis or thromboembolism confirmed by autopsy examination or tissue biopsy? (this includes pathologic evidence of microcirculation thrombosis). *If YES, specify location(s) in C*	☐ YES	☐ NO	☐ UNKNOWN
C0.3	Was thrombosis or thromboembolism confirmed by a surgery? *If YES, specify location(s) in C*	☐ YES	☐ NO	☐ UNKNOWN

C0.4	Was there a severe and persistent headache that onset from 5 to 30 days after vaccination (with the day of vaccination considered to be 'day 0')	☐ YES	☐ NO	☐ UNKNOWN

C Check all that apply	☐ 1. Deep Venous Thrombosis of leg(s)	☐ 8. Hepatic vein thrombosis	
	☐ 2. Deep Venous Thrombosis of arm(s)	☐ 9. Mesenteric vein thrombosis	☐ 15. Ischemic stroke due to arterial thrombosis
	☐ 3. Pulmonary thromboembolism	☐ 10. Splenic vein thrombosis	☐ 16. Myocardial infarction due to coronary artery thrombosis
	☐ 4. Cerebral venous thrombosis	☐ 11. Renal vein thrombosis	
	☐ 5. Cerebral venous sinus thrombosis	☐ 12. Adrenal vein thrombosis	☐ 17. Ischemic limb due to arterial thrombosis
	☐ 6. Jugular vein thrombosis	☐ 13. Retinal vein thrombosis	
	☐ 7. Portal vein thrombosis	☐ 14. Other non-listed venous thrombosis	☐ 18. Other non-listed arterial thrombosis

D. Symptom onset within a characteristic interval following vaccination (defined as Day 0)				
D1	Symptoms onset within the interval of 4 to ≤ 30 days after vaccination	☐ YES	☐ NO	☐ UNKNOWN
D2	Symptoms onset within the interval of 31 to ≤ 42 days after vaccination	☐ YES	☐ NO	☐ UNKNOWN
E. Anti-PF4 Antibody Present				
E0.1	Was an anti-PF4 antibody ELISA test done? If YES, answer E1 below.	☐ YES	☐ NO	☐ UNKNOWN
E1	Was the anti-PF4 antibody ELISA test positive? *Note: if the ELISA test was negative for anti-PF4 antibody, answer NO; if test result uninterpretable or unavailable answer UNKNOWN*.	☐ YES	☐ NO	☐ UNKNOWN
E0.2	Was a functional assay for PF-4 dependent antibodies done? If YES, answer E2 below	☐ YES	☐ NO	☐ UNKNOWN
E2	Was the functional assay positive for PF-4 dependent antibodies? *Note: if no PF4 dependent antibodies detected, answer NO; If test result uninterpretable or unavailable answer UNKNOWN*	☐ YES	☐ NO	☐ UNKNOWN
F. Clinical evidence for presence of thrombosis or thromboembolism. *NOTE: If C0.1, C0.2 or C0.3 = YES, and thrombosis location(s) identified in C above, there is no need to complete this section. It is only required if C0.1 and C0.2 and C0.3 = NO or Unknown*				
Complete both F1 and F2 sections below by selecting YES, NO or UNKNOWN for each of F1: 1 through 8 AND F2: 1 through 6.				

F1. Physician diagnosis of ≥1 thrombosis or embolism syndrome (check all that apply)	☐ 1. Deep Venous Thrombosis of limb(s)	☐ 5. Retinal vein thrombosis
	☐ 2. Pulmonary embolism (PE)	☐ 6. Non-hemorrhagic or ischemic stroke due to arterial thrombosis
	☐ 3. Abdominal vein thrombosis	☐ 7. Myocardial infarction due to coronary artery thrombosis
	☐ 4. Jugular venous, cerebral venous or cerebral venous sinus thrombosis	☐ 8. Other arterial thrombosis (arm or leg, aortic, renal, adrenal, optic)

F2. At least one characteristic clinical symptom or sign of thrombosis or embolism Check all that apply. Only one of the listed symptoms and signs need be present for each listed condition.	☐ 1**. Deep Venous Thrombosis.** ≥1 of: new onset swelling, usually but not always in lower extremities; localised swelling accompanied by pain and tenderness; reddened or discoloured or warm skin; pitting edema.
	☐ 2. **Pulmonary embolism.** ≥1 of: sudden onset of shortness of breath; pleuritic chest pain; cough; haemoptysis, tachycardia; arrhythmia; cyanosis; hypotension.
	☐ 3. **Abdominal vein thrombosis(hepatic, splenic, mesenteric, renal).** ≥1 of: sudden onset of acute abdominal pain, which may be out of proportion to physical exam findings; bloating; nausea; vomiting; diarrhoea; bloody stools; ascites; hepatomegaly
	☐ 4. **Renal arteries or veins thrombosis.** ≥1 of: flank pain; abdominal pain; nausea; vomiting; haematuria; decreased urine output
	☐ 5. **Adrenal arteries or veins thrombosis**. Features of adrenal insufficiency (fatigue, dizziness, nausea, vomiting, diarrhoea)
	☐ 6. **Jugular, cerebral or cerebral sinus venous thrombosis:** ≥1 of :new onset of unexplained headache, often severe, typically persisting; focal neurologic deficit(s) (e.g.: aphasia, dysarthria, difficulty with speech, vision or hearing, leg or arm weakness); encephalopathy; seizure; blurred vision; double vision
	☐ 7**. Ischemic stroke due to arterial thrombosis**. sudden onset of ≥1 focal neurologic deficit(s) (see 6. Above for examples)
	☐ 8. **Myocardial infarction.** ≥1 of: chest pain (often crushing in nature); shortness of breath; arrhythmias; cyanosis; sudden death
	☐ 9. **Ischemic limb or aortic thrombosis.** ≥1 of: cold pale limbs; loss of pulse
	☐ 10. **Retinal vein or optic artery thrombosis:** ≥1 of reduced or blurred vision; sudden painless loss of vision

X – Alternative diagnosis for clinical illness		
X1	Were any of the following conditions considered to be an alternative diagnosis for the clinical illness? Check all that apply	
	☐ 1. Heparin-induced thrombocytopenia (HIT)	☐ 4. Antiphospholipid syndrome
	☐ 2. Autoimmune or spontaneous HIT-like syndrome	☐ 5. Hemolytic uremic syndrome (HUS) due to *E. coli* 0157 or Shiga toxin

	☐ 3. Thrombotic thrombocytopenic purpura (PPT)	☐ 6. VITT-like syndrome due to autoimmune disease or viral infection ☐ 7. Dengue
X2	Were any of the following conditions considered to be an alternative diagnosis for the clinical illness? Check all that apply	
	☐ 1. Cancer-associated thrombosis and thrombocytopenia ☐ 2. Trauma associated thrombosis and thrombocytopenia ☐ 3. Thombosis in patients with hypo-proliferative thrombocytopenia due to cancer ☐ 4. Thrombosis in patients with liver disease the thrombocytopenia secondary to liver disease ☐ 5. Thrombosis in patients with thrombocytopenia due to alcohol abuse ☐ 6. Stroke or peripheral artery embolism in patients with atrial fibrillation and low platelet counts due to other reasons (e.g., liver disease)	☐ 7. Sepsis with DIC (e.g., meningococcemia) or thrombosis (e.g., aortic valve endocarditis ☐ 8. Severe pulmonary embolism with thrombocytopenia ☐ 9. Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome ☐ 10. Thrombosis in a pregnant woman with benign thrombocytopenia ☐ 11. Atypical HUS due to complement regulation defects ☐ 12. Thrombosis in a patient with hypo-proliferative thrombocytopenia due to Vitamin B deficiency or toxic drug effects ☐ 13. Thrombosis in a patient with hereditary thrombocytopenia ☐ 14. Paroxysmal nocturnal hemoglobinuria (PNH) ☐ 15. Cerebral malaria

Step 2. Based on clinical data entered in Step 1, assign a value to CD criteria A, B, C1, C2, D3 and F using the rules in Criterion Options columns

CRITERION					CRITERION VALUE: compare data entered in step 1 table to formulae in the YES, NO and UNKNOWN columns to determine FINAL VALUE for each criterion		
CLINICAL CATEGORY	Name	FINAL VALUE (Circle / Highlight)			Criterion = YES (Y) IF:	Criterion = NO (N) IF:	Criterion = UNKNOWN (U) IF:
Thrombocytopenia	A	Y	N	U	A1 or A2 or A3 = YES	A1 AND A2 AND A3 = NO	A1 AND A2 AND A3 = NO or UNKNOWN*
Thrombosis or thromboembolism confirmed by imaging, surgery or pathology	C1	Y	N	U	[C0.1 or C0.2 or C0.3 = YES) AND ≥1 of C(1-18) = YES]	[(C0.1 and C0.2 and C0.3 = NO)	(C0.1 and C0.2 and C0.3) = NO or UNKNOWN*
Pre-VITT	C2	Y	N or U		C0.4 AND B4 = YES	C0.4 or B4 not equal to YES	
Longer than usual interval from vaccination to onset in the setting of confirmed DVT or pulmonary embolism	D3	Y	N	U	C (1, 2 or 3) = YES AND None of C(4-18) = YES AND D2 = YES	≥1 of C (4-18) = YES AND D2 = YES	C0.1 and C0.2 and C0.3 = NO or UNKNOWN AND D2 = YES
Longer than usual interval from vaccination to onset in the setting of unconfirmed but clinical evidence for DVT or pulmonary	D4	Y	N	U	D2 = YES AND [F1 (1 or 2) OR F2 (1 or 2)] = YES AND None of [F1(3-8) AND F2 (3-10)] = YES	D2 = YES AND Any of [F1 (3-8) OR F2 (3-10)] = YES	D2 = YES AND None of [F1(1-8) AND F2 (1-10)] = YES
Clinical evidence of thrombosis or thromboembolism	F	Y	N or U		≥1 of F1 (1-8) OR F2 (1-10) = YES	None of [F1(1-8) AND F2(1-10)] = YES	

Alternate diagnosis to VITT	X1	Y	N or U	≥1 of X1 (1-7) = YES	None of X1 (1-7) = YES
Alternate diagnosis to VITT & TTS	X2	Y	N or U	≥1 of X2 (1-15) = YES	None of X2 (1-15) = YES

** NOTE: choose UNKNOWN if there is a combination of NO and unknown (e.g. if A1 = NO and A2 = NO and A3 = UNKNOWN then A = UNKNOWN)*

Step 3. Record the final value for Criteria B4, C0.4, D1, E1 and E2 from the step 1 table and for criteria A, C1, C2, D3, D4, F, X1 and X2 from the Step 2 table. Y = YES, N = NO, U = UNKNOWN

Criterion	A	B4	C0.4	C1	C2	D1	D3	D4	E1	E2	F	X1	X2
Final Value													

Step 4A Use the final values of all criteria recorded in the Step 3 Table above to determine the level of certainty based on the formulae below for VITT. Start with Level 1 (criteria A, B4, C1, C0.4, D1, D3, E1, E2). If Level 1 not met, then move to Level 2 (criteria A, B4, C1, C0.4, D1, D3, E1, E0.2, E2, X1, X2) and, if not met, try Level 3(A, B4, C1, C0.4, D1, D3, E1, E2, X1, X2). If none of Levels 1, 2 or 3 met, try Level 5 (criteria X1, X2). If Levels 1, 2, 3 and 5 not met, then assign Level 4. **NOTE: If Level 4 or Level 5, assess case for TTS.**

Level of Certainty		VITT
Level 1 can be met by either 1.1 or 1.2	1.1	[A AND B4 AND (C1 or C0.4) AND (D1 or D3) AND (E1 or E2) = YES]
	1.2	≥3 of [A OR B4 OR (C1 or C0.4) OR (D1 or D3) = YES] AND (E2 = YES)
Level 2		≥3 of [A OR B4 OR (C1 or C0.4) OR (D1 or D3) = YES] AND (E1 = YES) AND [(E0.2 OR E2 = NO or UNKNOWN] AND (X1 AND X2 = NO or UNKNOWN)
Level 3		≥3 of [A OR B4 OR (C1 or C0.4) OR (D1 or D3) OR (E1 or E2) = YES] AND (X1 AND X2 = NO or UNKNOWN)
Level 4		Reported VITT but fails to meet any level of certainty.
Level 5		X1 OR X2= YES (only applies to Levels 2 and 3. If case meets level 1, plausible alternative explanations don't exclude VITT)

Step 4B Use the final values of all criteria recorded in the Step 3 Table above to determine the level of certainty based on the formulae below for TTS. Start with Level 1 (criteria A, C1, C2, D1, D3, X2). If Level 1 not met, then move to Level 2 (criteria A, C1, C2, D1, D4, F, X2). If neither Levels 1 nor 2 is met, try Level 5 (criteria A, D1, D3, D4, C1, C2, F, X2). If Levels 1, 2 and 5 not met, then assign Level 4.

Level of Certainty	TTS
Level 1	(A = YES) AND (X2 = NO or UNKNOWN) AND (C1 or C2 = YES) AND (D1 or D3 = YES)*
Level 2	(A = YES) AND (X2 = NO or UNKNOWN) AND (C1 and C2 = NO or UNKNOWN) AND (D1 or D4 = YES)* AND (F = YES)

Level 3	There is no level 3 for TTS
Level 4	Reported TTS but fails to meet any level of certainty
Level 5	(A = NO) OR (X2 = YES) OR [(C1 and C2 = NO or UNKNOWN) AND (F = NO)]

** D1, D3 or D4 criteria only apply to the context of cases of suspect VITT that fail to meet VITT Level 1, 2 or 3 of diagnostic certainty and thus are being assessed using the TTS case definition. The criterion is not required for: a) studies of TTS background incidence; b) studies including unvaccinated individuals; cases being assessed not as VITT, but rather as one of the other immune-mediated causes of TTS, such as TTP or antiphospholipid syndrome. A specific vaccine to onset interval has not been determined for such cases; the time to onset following vaccination should be recorded but it is not part of the case definition.*

Figure1. Pictorial algorithm for determining VITT level of diagnostic certainty.

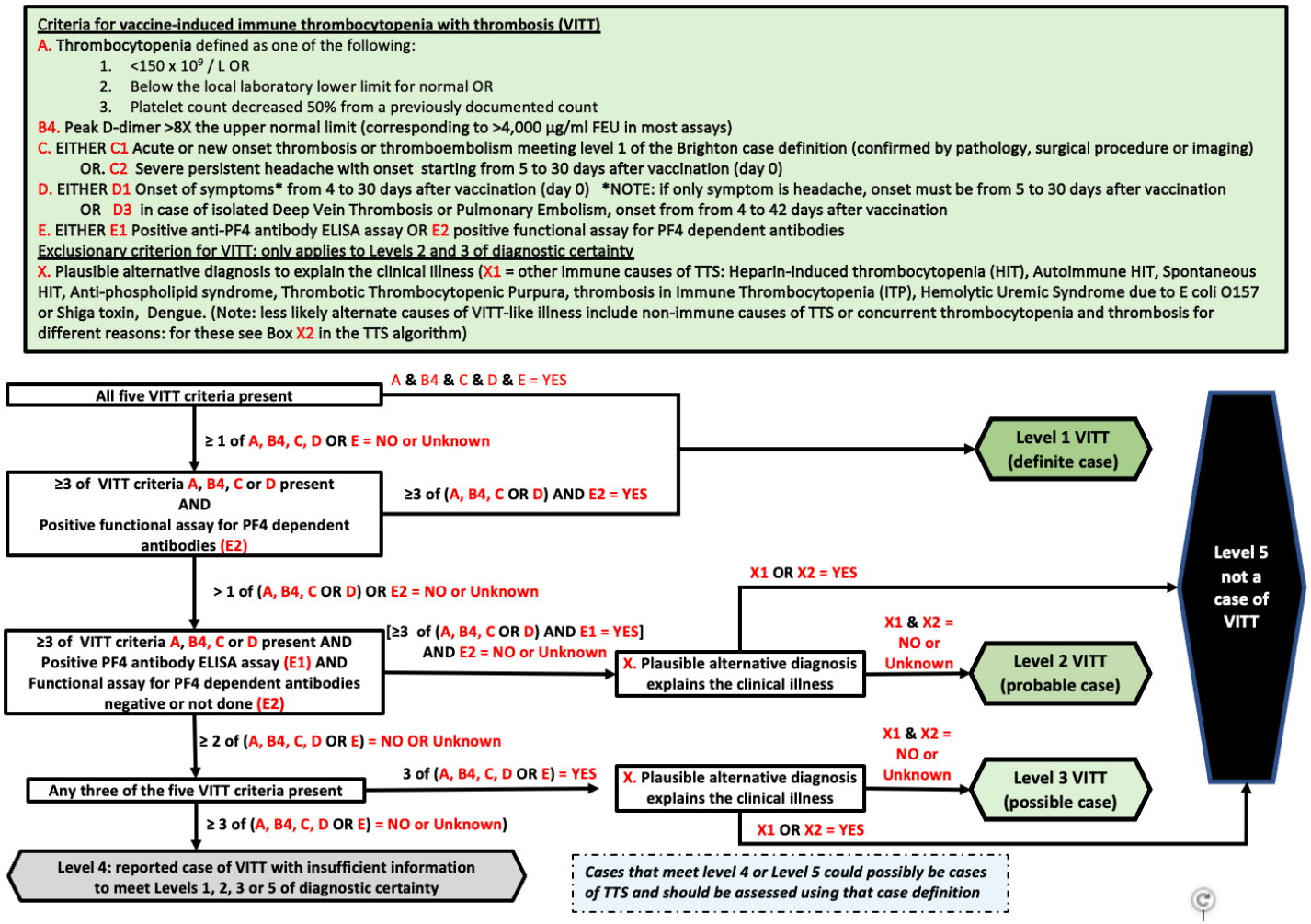
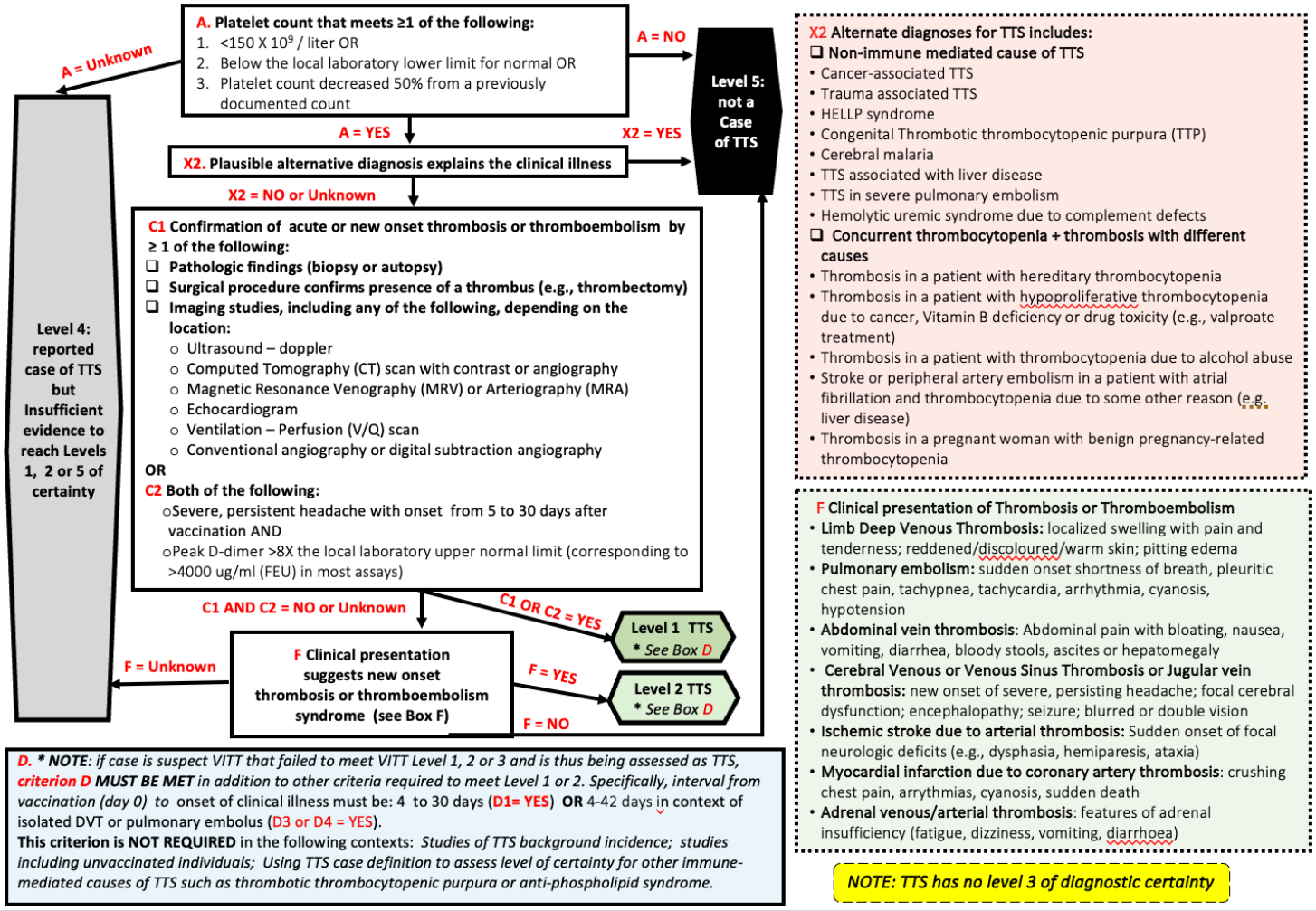


Figure 2. Pictorial algorithm for determining TTS level of diagnostic certainty



GLOSSARY OF TERMS

Term	Definition
Aphasia	Impairment of spoken language abilities that affect production and/or comprehension of speech
Anti-PF4 antibody	Antibody to Platelet Factor 4. There are two ways to measure anti-PF4 antibody: 1. ELISA test 2. Functional assay for PF4 dependent antibodies
Ascites	Excess abdominal fluid
D-dimer	Substance that serves as a marker of activation of both the coagulation and fibrinolytic systems, reflecting a degree of intravascular coagulation. D-dimer is generated after thrombin formation and subsequent degradation of cross-linked fibrin. Levels are often reported as fibrinogen equivalent units (FEU) with normal being <0.4 FEU which is equivalent to <250ng/mL. To meet the VITT criterion the D-dimer level must be >4000 mcg/mL which is >8 times the usual upper limit of normal.
Dysarthria	Difficulty in speech due to weakness of speech muscles
Encephalopathy	state of being in which consciousness or mental status is altered
Haemoptysis	Coughing up blood
Hepatomegaly	Enlarged liver
Pitting edema	A type of swelling that results in an indentation or 'pit' that remains after pressure is applied to the swollen área.
Pleuritic chest pain	Chest pain that is sudden, intense, sharp, stabbing or burning in nature; typically pain is made worse by breathing or coughing or sneezing or laughing.
Pre-VITT	VITT presentation where there is not yet evidence of thrombosis but there is a severe and persistent headache with thrombocytopenia. It is thought that in such cases, if management had been delayed, cerebral vein thrombosis, or cerebral venous sinus thrombosis would ensue.
Radiologic imaging study	In the context of VITT or TTS radiologic imaging studies are chosen based on the possible location of the thrombus or thromboembolism as described below: • Deep Venous Thrombosis of arm or leg: compression ultrasonography with and without Doppler; contrast catheter venography, Magnetic Resonance (MR) venography or Computed Tomography (CT) venography • Pulmonary thromboembolism: CT pulmonary angiography; V/Q scan (Ventilation Perfusion scan); contrast-enhanced MR angiography; digital-subtraction or conventional angiography • Cerebral venous thrombosis or cerebral venous sinus thrombosis: CT venography

	• Abdominal vein thrombosis (including portal, hepatic, mesenteric, splenic, renal or adrenal vein thrombosis): abdominal ultrasound with Doppler; CT scan with contrast; MR • Ischemic stroke due to arterial thrombosis: non-contrast CT; CT angiography; MRI; MR angiography

Annex 6

Methodology

6.1.VITT and TTS ICD-9/10-CM, MedDRA and SNOMEDCT Codes [2-6]

An initial set of codes were retrieved through the CodeMapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[2] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[3] CodeMapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9-CM, ICD-10-CM, and MedDRA.[4, 5] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[6] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMEDCT, MeSH, ICPC-2 and Read-CTv3. In this updated version of the Companion Guide, the SNOMEDCT codes have been added.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.
3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the CodeMapper concepts was reviewed by a medical expert (BL) familiar with the encephalitis Brighton case definitions for all Tier 1 AESI. The concepts identified for encephalitis were

considered relevant for background incidence rate determination as well as to study hypotheses related to encephalitis as a vaccine-product related reaction. Most of the terms include encephalitis and acute disseminated encephalomyelitis since encephalitis may be part of these broader categories.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the CEPI Developers' Toolbox and at the Brighton Collaboration website.

6.2. Literature search for VITT and TTS to support the Case Definition Working Group and inform the Companion Guide regarding Background rates[7-30] and Risk Factors[7,31-127]

Prior to the Working Group formation, the European Medicines Agency held a virtual workshop with topic experts on June 27, 2022 to review what was known at the time regarding the pathophysiology of Thrombosis with Thrombocytopenia (TTS) following adenovirus vector COVID-19 vaccination. The published meeting report[7] was reviewed and the list of citations hand searched as a start to gathering existing evidence that would inform the development of both case definitions and the associated companion guide.

Subsequently a simple search for articles with the term 'VITT' was done on Jan 10, 2023 and yielded a total of 359 articles. Articles were screened by a single medical reviewer (BL). There was 1 duplicate (published meeting report mentioned above[2]). Based on screening of title and abstract a total of 245 were excluded for the following reasons: 21 were completely unrelated to TTS or VITT; 30 were commentary or editorials; 40 focused on therapy; 13 focused on AESI other than VITT; 9 were non-English; 66 were case reports of VITT following ChAdOx1 or Ad26; 66 were published early during the evolution of understanding about VITT clinical presentation or diagnosis. The remaining 113 articles were reviewed in depth and notes taken. Ultimately 55 articles were considered contributory for, and thus used in the guide. The other 58 were excluded primarily because of the repetitive nature of what was presented in review articles covering VITT and TTS risk factors, clinical presentation and diagnosis. An additional 115 relevant articles were found on hand search of citations in the 113 articles that were reviewed in depth, or contributed by working group members.

6.3. VITT and TTS Risk Factors [1, 7, 31-127]

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:

1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for immune mediated TTS entities including VITT, HIT, TTP, APLS and ITP. Risk factors were included only if there was evidence supporting an association each entity.

6.4. TTS and VITT Case Definitions[1] key caveats for diagnosis, data analysis and presentation[1, 128-177]

The published Brighton case definition for TTS and VITT was reviewed and key aspects identified with particular relevance to real time assessment of TTS and VITT in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published TTS - VITT case definition was reviewed, and key recommendations identified for data collection, analysis and presentation specific to the adverse event reproduced or summarized. Finally, relevant evidence regarding real time investigation and diagnosis of VITT and other immune-mediated TTS syndromes were based on articles retrieved from the literature review or hand search of included article citations.

6.5. Data Abstraction & Interpretation Form, Tabular Checklist and Algorithms for Level of Certainty Determination

Data abstraction and interpretation forms along with the tabular and pictorial algorithms for determining Level of Certainty were drafted during the course of the Working Group meetings and revised as the case definitions were revised as part of ongoing Working Group discussions and following review of the proposed case definitions by subject matter experts and Brighton stakeholders. The same form, checklist and algorithms are used for the online digital version of the Automated Brighton Classification (ABC) tool.

Annex 7

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