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Thrombosis with thrombocytopenia syndrome (TTS) and vaccine-induced immune thrombocytopenia and thrombosis (VITT): Brighton Collaboration case definitions and guidelines for data collection, analysis, and presentation of immunisation safety data

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ABSTRACT

This is a revision of the online November 2021 Brighton thrombosis with thrombocytopenia syndrome (TTS) case definition and a new Brighton Collaboration case definition for vaccine-induced immune thrombocytopenia and thrombosis (VITT). These case definitions are intended for use in clinical trials and post-licensure pharmacovigilance activities to facilitate safety data comparability across multiple settings. They are not intended to guide clinical management.

The case definitions were developed by a group of subject matter and Brighton Collaboration process experts as part of the Coalition for Epidemic Preparedness Innovations (CEPI)-funded Safety Platform for Evaluation of vACcines (SPEAC).

The case definitions, each with defined levels of diagnostic certainty, are based on relevant published evidence and expert consensus and are accompanied by specific guidelines for TTS and VITT data collection and analysis. The document underwent peer review by a reference group of vaccine safety stakeholders and haematology experts to ensure case definition useability, applicability and scientific integrity.

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Table 1
Key objectives for Brighton Collaboration case definitions and formats to achieve them [2,3].

Objective	Case definition format to meet objective
Enable comparability and *meta*-analysis of safety data throughout the vaccine life cycle and across all resource settings.	• Tiered in up to three levels of diagnostic certainty from most specific/least sensitive (Level 1) to least specific/most sensitive (Level 3). The levels do not reflect clinical severity or seriousness. Based on scientific evidence and consensus from a group of subject matter and Brighton Collaboration process experts Include guidelines on data collection and analysis specifically relevant to the adverse event being defined. Enable classification of all cases even if case definition not met: Meets case definition at Level 1, 2 or 3 of diagnostic certainty Fails to meet any level of certainty because of missing data (Level 4) Not a case because exclusion criterion met or necessary criterion known to be absent (Level 5)
Provide a definition that can be applied equally to exposed and non-exposed groups.	• Interval from exposure (immunisation) to adverse event onset is not a criterion for the case definition, unless it is specific to a known vaccine-event causal association (e.g., generalised vaccinia following exposure to vaccinia virus)
Avoid use in unintended settings such as clinical case management	• Response to treatment not included as a case definition criterion

1. Introduction

This paper is a revision of the most recent version (November 2021) of the draft Brighton Collaboration case definition for thrombocytopenia with thrombosis syndrome (TTS) [1]. It also provides a new Brighton Collaboration case definition for vaccine-induced immune thrombocytopenia and thrombosis (VITT), which is consistent with existing definitions from other authorities.

2. Rationale for revising the TTS case definition and developing a new Brighton Collaboration case definition for VITT

Standard harmonised case definitions are crucial in facilitating collection of valid, reproducible vaccine safety evidence. This is the overarching goal of Brighton Collaboration case definitions as described in Table 1 [2,3].

Fig. 1 shows the timeline from first recognition of TTS following adenovirus-vectored COVID-19 vaccination to development of initial case definitions and guidelines and growing evidence elucidating the pathogenesis of VITT [1,4–21].

TTS is a broad syndrome that may be triggered through different mechanisms (e.g., immune-mediated and non-immune mediated) and VITT can be considered as one of several entities that fall under the umbrella of immune-mediated TTS. Since VITT is a specific entity with known pathogenesis requiring specific laboratory testing for confirmation, the case definition criteria may not be achievable in low resource settings. TTS is less dependent on specific testing and thus may be more readily confirmed in low resource settings.

3. Methods for development of TTS and VITT case definitions

A Brighton Collaboration TTS – VITT Working Group was formed in March 2023 and included seven subject matter experts in hematology and transfusion medicine, and more specifically TTS and VITT (AG, LS, SP, MP, HT, VC, DG), one in paediatric intensive care (Amir Navaei), and three in vaccinology and Brighton Collaboration processes for case definition development and format (FM, JB, BL).

To support the development of the case definition, guidelines and complementary companion guide, literature searches were performed to find existing TTS and VITT case definitions and diagnostic methods, as well as articles on epidemiology with particular attention to descriptions of clinical presentations, studies of background incidence and risk factors including coincidental and vaccine-related causes. Full methods and results for all systematic searches are presented in the companion guide which will be posted on the SPEAC (Safety Platform for Emergency Vaccines) Zenodo Community site [22]. The results were screened to identify potentially relevant articles for the case definition and guidelines. These were made available to the Working Group members who reviewed them to select those considered most pertinent to their decision-making process for the development of the case definition and guidelines.

To ensure the scientific soundness, applicability and usefulness of the TTS and VITT case definitions, a reference group of key stakeholders from high, middle and low healthcare resource settings, was asked to review the draft case definition criteria and levels of certainty and to provide their feedback using an on-line questionnaire. The Working Group reviewed and incorporated the feedback into the final case definition. Additionally, the penultimate draft manuscript was reviewed by independent subject matter experts in TTS and VITT prior to finalising the case definition. The questionnaire, reference group feedback and working group responses are available in the Supplementary Material to this publication [Link].

4. Background relevant to TTS and VITT case definitions

As shown in Fig. 1, a safety signal that was first recognised as a syndrome of concurrent thrombosis and thrombocytopenia, was shown to be mediated by platelet activating anti-platelet factor 4 (PF4) antibodies. Many names were proposed for this syndrome during the evolution of the analysis of the safety signal, including TTS and VITT. As discussed further below (Section 4.1.3), TTS is a term that encompasses many different entities with varying pathogenesis. One of those entities is VITT, which is now understood to be a clearly defined syndrome associated with anti-PF4 antibodies induced by at least two of the COVID-19 adenovirus-vectored vaccines (ChAdOx1.S and Ad26.COV2.S) [21,23]. As such, specific criteria are required to define VITT, some of which require resources that may not be available in low resource settings. Accordingly, the Working Group decided to define both TTS and VITT. Where possible, the VITT case definition should be used first to assess potential cases, but if no level of the case definition can be met, the TTS case definition should be used. Given the overlap in case definition criteria for VITT and TTS, and to avoid duplication of relevant information, this section presents background information relevant to both TTS and VITT, and to each entity separately.

4.1. Background relevant for both TTS and VITT

Case definitions developed by various organisations as the TTS safety signal emerged during the mass COVID-19 vaccination campaigns are summarised in Table 2 [1,20,24,25]. Several of the criteria included in Table 2 have also been adapted and adopted in the Brighton Collaboration TTS and VITT case definitions, as described in Sections 6 and 7.

4.1.1. Thrombocytopenia

The 2007 Brighton case definition for thrombocytopenia is based on a platelet count of < 150 X 10^9/L [26]. However, platelet counts between 100 and 149 x10^9/L can be physiologically normal among individuals of certain race and in older adults [27]. In addition, certain haematological diseases such as chronic immune thrombocytopenia (cITP) or liver disease are associated with a baseline platelet count that

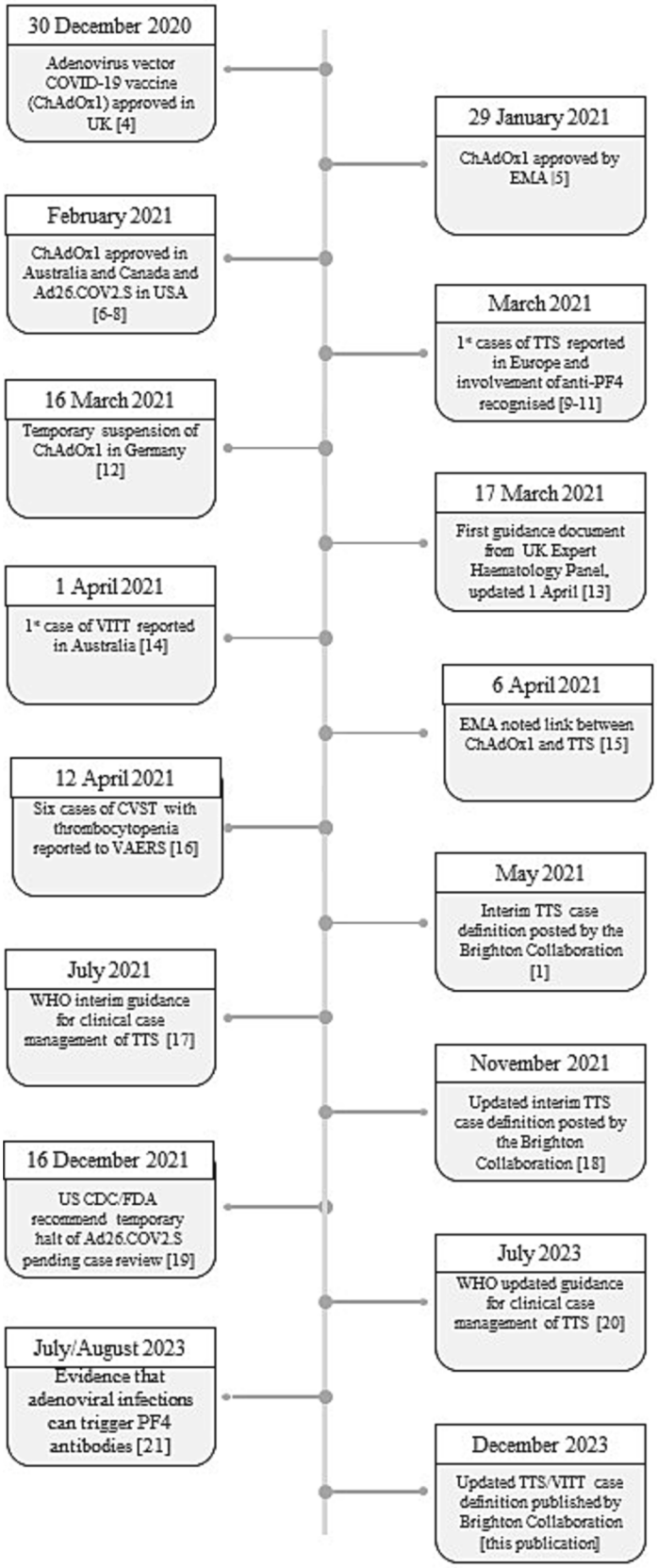

Fig. 1. Timeline of initial recognition of TTS signal during COVID-19 vaccine campaign, creation of case definitions and understanding regarding the pathogenesis of VITT.

Table 2
Existing case definitions for TTS and VITT. Criteria in bold have been included in the Brighton Collaboration VITT and TTS case definitions.

Level of certainty	World Health Organisation 2023 [20] TTS	Centres for Disease Control and Prevention [24] TTS	Brighton Collaboration [1] TTS	UK Expert Haematology Group [25] VITT
Definite, or confirmed	• **Confirmed thrombosis**[1] in an uncommon location (cerebral or splanchnic veins) OR in multiple locations with platelets < 50 x 10^9/L AND peripheral smear showing reduced platelets with no evidence of platelet clumping AND ≥ 1 of: **positive anti-PF4 antibodies by ELISA or functional assay** **D-dimer > 4000 ng/mL** OR **Confirmed thrombosis**[1] in any location with **platelets < 150 x 10^9/L** AND **positive anti-PF4 antibodies by ELISA or functional assay**	**Platelets < 150 x 10^9/L** AND Thrombosis in an unusual location[4] *(positive anti-PF4 ELISA antibody test supportive but not required)*	**Platelet count < 150 x 10^9 /L**, that is new onset AND with no heparin exposure within last 30 days AND ≥ 1 of the following: **confirmed thrombosis**[1] in any location **severe, persistent headache ≥ 5 days post vaccination AND D-dimer > 8 x ULN** **suggestive thrombosis**[2] AND ≥ 1 of: **D-dimer ≥ 4 x ULN** **Anti-PF4 by ELISA** **Anti-PF4 by functional assay**	**Meets all five criteria below:** **1. onset of symptoms 5–30 days after COVID-19 vaccine or up to 42 days if thrombotic event isolated DVT or PE** **2. presence of thrombosis** **3. platelet count < 150 X 10^9/L** **4. positive anti-PF4 antibody by ELISA assay** **5. D-dimer > 4000 ng/mL**
Probable	• **Confirmed thrombosis**[1] in uncommon or multiple locations AND (platelets from 50 to < 150 x 10^9 /L **OR > 50 % decrease from baseline) AND D-dimer > 4000 ng/mL** OR **Confirmed thrombosis**[1] in a common location OR **suggestive thrombosis**[2] **OR** [3] AND platelets < 50 x 10^9 /L AND **D-dimer > 4000 ng/mL**	**Platelets < 150 x 10^9/L** AND thrombosis in common location[5] AND positive anti-PF4 ELISA antibody test	**Platelet count < 150 x 10^9 /L,** that is new onset AND with no heparin exposure within last 30 days AND ≥ 1 of the following: **suggestive thrombosis by supportive imaging**[3] OR D-dimer > ULN **suggestive thrombosis by clinical syndrome**[4]	i. Three of criteria 1, 2, 3 and 4 met AND criterion 5 met OR ii. Criteria 1, 2, 3 and 4 all met but D-dimer unknown or 2000–4000 ng/mL
Possible	**Confirmed thrombosis**[1] in common location AND (platelets from 50 to < 150 x 10^9 /L OR > 50 % decrease from baseline) AND **D-dimer > 4000 ng/nL or no D-dimer tested**	Not applicable	**Platelet count < 150 x 10^9 /L**, that is new onset AND with no heparin exposure within last 30 days AND **suggestive thrombosis based on clinical syndrome**[3]	Two to three of criteria 1, 2, 3 and 4 met but D-dimer unknown or 2000–4000 ng/mL

CVST: cerebral venous sinus thrombosis; CVT: cerebral vein thrombosis; DVT: deep vein thrombosis; PE: pulmonary embolism.
[1] Thrombosis demonstrated by imaging study or surgical or pathology findings; [2] Thrombosis suggested but not proven by supporting imaging; [3] Thrombosis suggested by presence of specific clinical syndromes consistent with thrombosis or thromboembolism (CVST, CVT, DVT, PE, splanchnic thrombosis, ischemic stroke, arterial thrombosis, MI); [4] CVS, portal vein, splenic vein, other rare venous and arterial thromboses; [5] Excluding isolated acute MI or ischemic stroke.

is lower than the normal reference range (RR) for affected individuals. Conversely, certain individuals can have a high level of normal platelet count (e.g., RR, 150–450x10^9/L) or have a haematological disorder, such as myeloproliferative neoplasms where their baseline platelet level is above the normal RR. The platelet counts in these individuals, if they have VITT or TTS, can be substantially reduced from their historical baseline (>50 %) but it will still be within the normal range [28].

4.1.2. Thrombosis and thromboembolism

Thrombosis in VITT and TTS can affect both the microcirculation and macrocirculation. The many possible sites for venous and arterial thrombosis are discussed further in section 4.3.2. The 2022 Brighton case definition for thrombosis and thromboembolism provides relevant background information including preferred diagnostic modalities depending on body location [29]. All three levels of certainty of the VITT case definition and the first level of certainty of the TTS case definition require that the thrombosis or thromboembolism be confirmed by imaging, histopathology or surgery (matching Level 1 of certainty of the published Brighton case definition). TTS Level 2 of certainty requires a typical clinical presentation, matching Level 3 of the published thrombosis and thromboembolism case definition. For both TTS and VITT, presence of a severe and persistent headache with an onset from 5 to 30 days after vaccination is an accepted alternative way to meet the thrombosis criterion. This situation has been termed pre-VITT and is discussed further in section 4.3.2.

4.1.3. Thrombocytopenia with thrombosis syndrome (TTS)

TTS has many possible causes which vary in frequency and pathogenesis which can be immune-mediated or non-immune-mediated (Table 3) [29]. VITT is in the category of immune-mediated entities. Some of the conditions in Table 3 can be easily recognised clinically, whereas others are more difficult to diagnose and may require specific laboratory assays (see Supplementary Material).

4.1.4. D-dimer

D-dimers are generated after thrombin formation and subsequent degradation of cross-linked fibrin, and thus reflect the degree of intravascular coagulation and can, therefore, serve as a global marker of activation of the coagulation and fibrinolytic systems. There are several commercial D-dimers assays available that use monoclonal antibodies to identify a specific epitope on cross-linked D-dimer molecules that is absent from fibrin monomers or fibrinogen. Assay types include enzyme-linked immunosorbent assays (ELISA), immunofluorescent assays, and latex agglutination assays and can be used for plasma, serum or whole blood samples.

The normal concentration of D-dimer is defined by the assay used, and commonly expressed as < 500 ng /mL fibrinogen equivalent units (FEU), which is equivalent to < 250 ng/mL D-dimer units (DDU). However, given the wide interlaboratory variation in assay methods, a threshold of more than eight times the upper limit of normal (ULN) for the assay and the laboratory may be more appropriate to use. The threshold refers to the peak level, as this may be higher than at presentation if treatment is delayed or if disease is progressing despite treatment.

Patients with definite (Level 1) VITT have D-dimer levels > 4000 ng/mL or more than eight times the ULN. Depending on the fulfilment of the other four VITT criteria (see Section 7) it is still possible to reach probable (Level 2) or possible (level 3) level of diagnostic certainty for VITT with D-dimer levels that are ≤ 4000 ng/mL. Typically, a normal or only mildly elevated D-dimer level would indicate that the patient does not have VITT and alternative diagnoses should be considered. However, reduced D-dimer levels may be caused by low grade disease, a test taken after treatment started when the condition is improving, or potentially, if the patient is already on anticoagulation for other reasons.

Table 3
Immune-mediated and non-immune-mediated thrombocytopenia with thrombosis syndromes.

Frequency	Immune-mediated TTS	Non-immune-mediated TTS
Frequent		Cancer-associated thrombosis and thrombocytopenia Trauma associated thrombosis and thrombocytopenia 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) Septicaemia with DIC (e.g., meningococcemia) or thrombosis (e.g., aortic valve endocarditis)
Uncommon	Antiphospholipid syndrome	Severe pulmonary embolism with thrombocytopenia
	Heparin-induced thrombocytopenia (HIT)	Haemolysis, Elevated liver enzymes and low platelets (HELLP) syndrome
	Thrombosis in immune thrombocytopenia (ITP)	Thrombosis in a pregnant woman with benign pregnancy-related thrombocytopenia
Rare	Vaccine-induced immune thrombocytopenia and thrombosis (VITT)	Congenital TTP
	Hemolytic uremic syndrome (HUS) due to *E. coli* 0157 or Shiga toxin	Atypical HUS (due to complement regulation defects)
	Thrombotic thrombocytopenic purpura (TTP)	Thrombosis in a patient with hypo-proliferative thrombocytopenia Vitamin B deficiency Toxic drug effects (e.g., valproate treatment)
	Autoimmune or spontaneous heparin-induced thrombocytopenia (aHIT, sHIT)	Thrombosis in a patient with hereditary thrombocytopenia
	Autoimmune or post viral infection VITT [21,23]	Paroxysmal nocturnal haemoglobinuria (PNH)
Geographic variation	Dengue	Cerebral malaria

4.2. Background relevant for TTS

4.2.1. Pathophysiology / pathogenesis

The pathophysiology and pathogenesis of TTS is poorly understood, except for VITT. It is more likely that there is a coincidental association between the comorbidities and vaccination rather than a causal association. Nonspecific proinflammatory consequences of vaccination, e.g., with resulting transient rise in fibrinogen and von Willebrand factor levels, could predispose to venous or arterial thrombotic events in otherwise susceptible individuals, but this would not usually be associated with thrombocytopenia. Both adenovirus vector-based and mRNA-based COVID-19 vaccines can induce platelet autoantibodies [30]. A recent study suggests that a subgroup of platelet autoantibodies can cause Fc-receptor dependent platelet activation, leading to intravascular platelet activation, formation of procoagulant platelets and manifestation of thrombosis [31]. Importantly, these patients all had a negative result for platelet activating anti-PF4-IgG.

4.2.2. Diagnosis of TTS syndromes

Diagnosis of TTS requires the presence of thrombocytopenia, defined as a platelet count $< 150 \times 10^9$/L, a count below the local laboratory lower limit for normal, or a ≥ 50 % decrease from a previously documented (recent, if possible) count, the exclusion of pseudo thrombocytopenia, and objectively documented thrombosis (e.g., by ultrasonography, CT, MRI, angiography).

The other features seen in VITT may or may not be present. The aetiology of TTS may be immune or non-immune (Table 3). TTS syndromes comprise a broad range of diagnoses and specific testing is further described in the Supplementary Material. It should be noted that the presence of one of the specific diagnoses listed in the Supplementary Material, would not exclude that the event under investigation was vaccination-induced, e.g., there are reports of thrombotic thrombocytopenic purpura (TTP) and anti-phospholipid syndrome (APS) triggered by vaccination [32,33].

4.3. Background relevant for VITT

The following sections focus on key evidence for the construction of the VITT case definition and the development of the associated guidelines.

4.3.1. Epidemiology of VITT including vaccine-associated causality

Two adenoviral vector-based vaccines have been implicated in VITT: ChAdOx1 nCoV-19 (produced by AstraZeneca, University of Oxford, Serum Institute of India); and Ad26.COV2.S (produced by Janssen, Johnson & Johnson) [34]. There are limited data available for the Gam-COVID-Vac/Sputnik V vaccine (produced by Gamaleya Institute), though cases of possible VITT have been reported related to this vaccine [35]. A single case of possible VITT has been reported related to the mRNA-1273 vaccine (produced by Moderna) and another related to the Gardasil 9 vaccine for human papillomavirus [36,37]. Caution should be used in interpreting these discrete cases since they may represent the background rate of spontaneous heparin-induced thrombocytopenia (which also involves platelet activating anti-PF4-IgG), viral-infection associated VITT, or other types of TTS also unrelated to vaccination [21,23,38,39].

It is challenging to determine the incidence of VITT, as this depends on accuracy of case ascertainment, the estimated size of the vaccinated population and the accurate recording of vaccine dose number. Data fidelity varies by jurisdiction. Moreover, few jurisdictions report definite cases of VITT following vaccination, using case definitions based on contemporary evolving evidence; the broader diagnostic category of TTS is more commonly reported. Estimates of the risk of TTS following adenoviral vector COVID-19 vaccination range from 1 case per 26,500 first doses of ChAdOx1 nCOV-19 administered (reported in Norway) to 1 case per 261,000 doses of Ad26.COV2.S administered (reported in the United States) [32,40]. The risk of VITT after second and subsequent doses of ChAdOx1 nCoV-19 appears to be far lower; 2.1 cases per million second doses (reported in the UK) and 2.2 cases per million second doses (reported in Australia) [41,42].

There are no known risk factors for VITT other than young age [43,44]. Sex, and medical comorbidities (including history of thrombosis) have no apparent impact on the risk of occurrence.

Drawing a causal link between a vaccine and specific adverse events of special interest (AESIs), such as VITT, based on WHO causality criteria requires a clear temporal relationship, strength of the association, a dose response relationship, consistency of evidence, specificity and biological plausibility and coherence [45]. VITT satisfies across multiple settings the temporal relationship, strength of association for two adenoviral-vectored vaccines and consistency of evidence. The development of this specific VITT case definition also enables clear biological plausibility and coherence with the detection of PF4 specific antibodies and/or functional activity consistent with proposed pathophysiology [46,47]. There is no clear dose–response, as the vaccine dose does not vary. The

Table 4
Case definition and levels of diagnostic certainty for thrombocytopenia with thrombosis (TTS).

Level 1 (definite case)	
1.1	**Thrombocytopenia indicated by ≥ 1 of the following:** • $<150 \times 10^9$/L • Below local laboratory lower limit for normal • ≥50 % decrease from a previously documented count **AND**
1.2	**Presence of ≥ 1 of the following:** • Acute or new onset thrombus or thromboembolism confirmed by imaging, surgical procedure or pathological examination of autopsy or biopsy material. • Severe, persistent headache with an onset from 5 to 30 days after vaccination with peak D-dimer > 8 x ULN (corresponding to > 4000 ng/mL) **AND**
1.3	**Symptom onset from 4 to 30 days after vaccination* (day 0).** • If the thrombosis is only DVT or pulmonary embolism, the interval can be up to day 42. **AND**
1.4	**A more plausible alternative explanation for illness not found**
Level 2 (probable case)	
2.1	**Thrombocytopenia (same as defined in 1.1 above)** **AND**
2.2	**Clinical presentation that is consistent with acute or new onset thrombosis or thromboembolism syndrome** **AND**
2.3	**Symptom onset from 4 to 30 days after vaccination* (day 0).** • If the thrombosis is only DVT or pulmonary embolism the interval can be up to day 42. **AND**
2.4	**A more plausible alternative explanation for illness not found**

* Except for severe and persistent headache which should have an onset from 5 to 30 days after vaccination

risk of VITT decreased with each subsequent dose, a counterintuitive phenomenon that is not yet well understood. Accordingly, all major regulatory agencies and the manufacturers of ChAdOx1 nCoV-19 and Ad26.COV2.S include VITT/TTS as a rare known risk of these vaccines in the product information [48,49].

4.3.2. Clinical presentations

VITT typically presents with onset of thrombosis-induced symptoms at day 5–30 after vaccination [20]. This may extend to 42 days post-vaccination where the thrombotic site is deep vein thrombosis or pulmonary embolism. One recent systematic review reported proven cases of VITT with symptom onset as early as 4 days following vaccination, which was consistent with the professional experience of the expert haematologists in the Working Group [50]. The Working Group pointed out the exception of headache onset, which should be from 5 to 30 days following vaccination, since headache is frequently reported just after vaccination and day 4 could result in frequent overlap with clinically-harmless early onset headache [51]. Thrombosis often affects multiple vascular beds, including arterial and venous micro- and macro-circulations, and unusual sites such as the splanchnic circulation (i.e., involving spleen, mesenteric, portal, renal, or adrenal veins). Cerebral vein thrombosis affects 50 % of patients with one third of these developing secondary intracerebral haemorrhages. Mortality rates are very high; in the first cases reported in Europe the mortality rate was about 50 % [9–11]. However, with raised awareness and prompt management, mortality has been reduced to about 5 % in Australia [52]. Pre-VITT (also known as VIT) may occur, where headache and thrombocytopenia are seen but thrombosis is not yet present [53,54].

The case definition criteria (see Section 7) are used to determine the likelihood of VITT. There are three situations where VITT is unlikely: i) thrombocytopenia without thrombosis and D-dimer < 2000 ng/mL; ii) thrombosis without thrombocytopenia and D-dimer < 2000 ng/mL (regardless of anti-PF4 antibody results); and iii) an alternative diagnosis is more likely.

4.3.3. Pathogenesis of VITT

VITT is a prothrombotic disorder caused by anti-PF4 antibodies activating platelets via the FcγIIA-receptor leading to thrombosis and thrombocytopenia. Pathophysiology and clinical manifestations of VITT are similar to those of HIT, however, differences between both disorders are relevant for diagnosis and treatment. In HIT, heparin binds to the ring of positively-charged amino acids at the equatorial region of the PF4 tetramer. This induces a conformational change and exposure of the antibody binding site at the polar region of PF4 tetramer.

In VITT, heparin-independent VITT antibodies bind to the same equatorial region of PF4 as heparin [55]. Heparin will inhibit the binding of these VITT antibodies to PF4 by blocking the antibody binding sites [55]. In both HIT and VITT, rapid antibody production within 5–10 days indicates a secondary immune response. In HIT, bacteria-PF4 complexes are most likely the primary immune trigger. The primary immune trigger for VITT is unknown. Both VITT- and HIT-antibodies cause FcγIIA receptor-mediated activation of platelets, neutrophils and monocytes, which exposes phospholipids on the surface of blood cells that then catalyse the activation of the coagulation cascade. In addition, neutrophils and monocytes release DNA, extracellular traps (NETs), which are also highly prothrombotic [56]. Indirectly these mechanisms also activate endothelial cells. Activated monocytes and endothelial cells express tissue factor, which results in further thrombin generation. Activated endothelial cells release von Willebrand factor which drives the prothrombotic process by binding PF4 and anti-PF4 antibodies, resulting in further activation of platelets and neutrophils.

The trigger for the anti-PF4 immune response in VITT is still unknown. Adenovirus-derived hexon proteins might play an important role, as they form charge-driven complexes with PF4 [57,58]. In addition, patients have been reported to present with a VITT-like disorder between 1 and 2 weeks after adenovirus infection, with the presence of thrombocytopenia, high D-dimer levels, thrombosis at unusual sites, and high titres of platelet activating antibodies [21,23,59,60]. VITT-like disease has also been reported following other viral infections, such as common colds, respiratory syncytial virus (RSV) infections and urinary tract infections [23]. Other constituents of the vaccine such as proteins derived from the cell lines in which the adenovirus vector is propagated and ethylene diamine tetra acetate (EDTA) in the ChAdOx1 vaccine contribute to a pro-inflammatory milieu, which may contribute to the anti-PF4 response [56].

The main treatments, i.e., therapeutic doses of anticoagulants and high-dose intravenous immunoglobulins, interfere with the pathogenesis of VITT by inhibiting thrombin generation and blocking FcγIIA receptor-mediated blood cell activation. In addition to anti-PF4 antibodies, at least 30 % of patients have anti-platelet autoantibodies which might aggravate thrombocytopenia in some VITT patients via an ITP-like mechanism [61].

4.3.4. Anti-PF4 ELISA and functional antibody testing to diagnose VITT

Detection of platelet-activating anti-PF4 antibodies in patient serum or plasma, enables a definitive diagnosis of VITT in the appropriate clinical context, given its pathogenesis [62]. ELISA-based antigen detection assays are recommended to confirm or exclude the presence of anti-PF4 antibodies. Commercial ELISAs in which PF4 antigen is complexed with a polyanion, developed to detect HIT antibodies are available, and un-complexed PF4 solid and fluid phase ELISAs can also be used [9,63,64]. Rapid antigen tests for HIT diagnosis, such as chemiluminescence immunoassays (CLIAs), lateral flow assays and particle gel immunoassays, do not detect VITT antibodies and should not be used [65]. The sensitivity and specificity for pathogenic VITT antibodies of the different ELISA platforms vary with sensitivity reported to be between 64 % and 100 % [63,64,66]. Variations between the optical densities (ODs) are also seen between ELISA platforms, thus, depending on the platform, low OD does not exclude VITT, although an OD > 2.0 is specific for VITT in the appropriate clinical context [63].

However, non-pathogenic anti-PF4 antibodies are present in 5 to 8 %

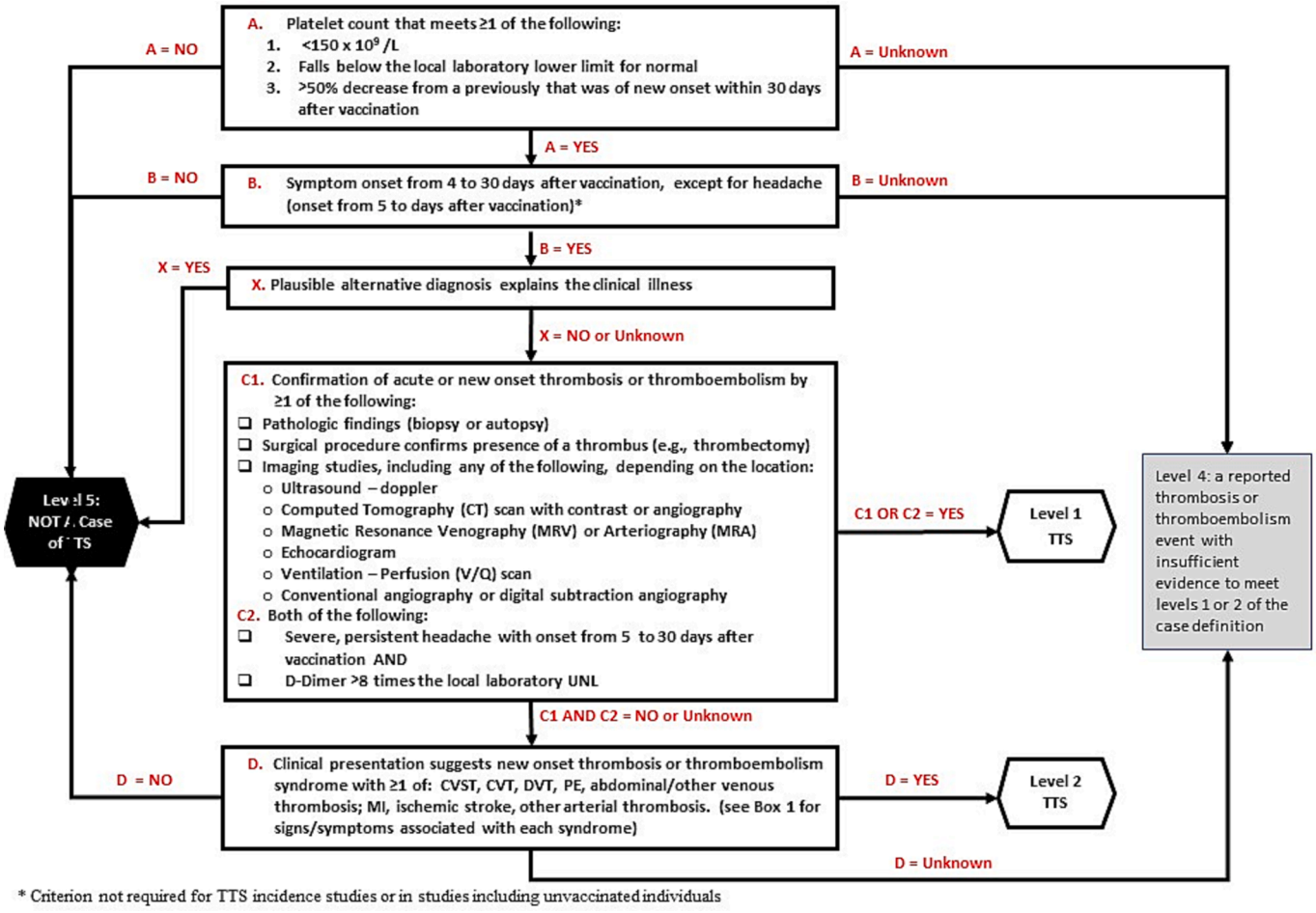

Fig. 2. Algorithm for levels of diagnostic certainty for acute or new-onset thrombocytopenia with thrombosis syndrome.

of healthy blood donors, patients with periodontal disease and individuals vaccinated with COVID-19 vaccines in the absence of VITT or TTS [67–73]. These non-pathogenic antibodies do not activate platelets, unlike pathogenic antibodies that can activate platelets and other thrombosis driving cells, leading to the thrombosis and platelet consumption that characterises VITT and TTS [69].

Functional assays are used to determine if anti-PF4 antibodies are pathogenic. In patients with post-vaccination thrombocytopenia and thrombosis who have high D-dimer but in whom anti-PF4 antibodies are not detectable by ELISA, a functional assay can be used to confirm the diagnosis of VITT [43]. Most functional assays aim to demonstrate that patients' plasma or serum induce platelet activation and a procoagulant phenotype in FcγIIA-reactive donor platelets by blocking the FcγIIA receptor, in the absence of exogenous heparin. The majority of these assays are HIT functional assays that have been modified to increase sensitivity for detection of the VITT PF4 antibodies and include PF4-^{14}C-serotonin release assay (PF4-^{14}C-SRA), and washed platelet functional assays such as the PF4-induced platelet activation (PIPA) and PF4-induced flow cytometry-based platelet activation (PIFPA) assays, whole blood procoagulant platelet assays with or without exogenous PF4 [74–77]. Common modifications include addition of exogenous PF4 to increase sensitivity and patient serum dilution 1 in 4 in case of a negative assay to achieve an optimal ratio for immune-complex formation between PF4 and anti-PF4 antibodies [62]. Given that heparin can compete with VITT-specific anti-PF4 antibodies for binding to the same PF4 binding sites, exogenous heparin should not be added to the functional assays as this can inhibit platelet activation by VITT antibodies and can prevent the detection of VITT cases [9,78].

The sensitivity and specificity of VITT diagnostic assays are dependent on the prevalence of disease within the tested population, thus VITT ELISA and functional testing should only be performed when there is a clinical suspicion for VITT, not as a screening test, given that the background prevalence of non-pathogenic (non-platelet activating) anti-PF4 antibodies post-COVID-19 vaccination is 5–8 % [67,70–73].

5. Rationale for Working Group decisions about the case definitions of VITT and TTS

5.1. Rationale for separate case definitions for VITT and TTS

The rationale for an updated case definition for TTS is primarily to enable classification of suspected cases in settings that have limited access to ELISA and functional PF4 antibodies testing.

5.2. Rationale for clinical and laboratory criteria

The case definitions for both TTS and VITT are consistent with other existing case definitions (Table 2) as well as with the published Brighton Collaboration case definitions for thrombocytopenia with thrombosis and thromboembolism, with some modifications [26,29]. Specifically, the definition of thrombocytopenia has been expanded to include regional variations in the lower limit of normal for platelet count and the possibility of a platelet count that is above the usual threshold of 150 x 10^9/L if this represents a > 50 % decrease from a chronically-high baseline count.

Severe persistent headache with an onset from 5 to 30 days after vaccination is accepted as an alternative criterion for thrombosis or thromboembolism for all levels of the VITT case definition but,

Table 5
Signs and symptoms of venous or arterial thrombosis syndromes by location.

Location	Signs and symptoms
Cerebral vein thrombosis, cerebral venous sinus thrombosis or jugular vein thrombosis	New onset of unexplained headache, often severe, typically persisting; focal cerebral dysfunction; encephalopathy; seizure; blurred vision; double vision
Deep vein thrombosis	New onset swelling usually but not always in lower extremities; localised swelling accompanied by pain [may be crampy in nature] and tenderness; reddened/ discoloured/warm skin; pitting oedema
Pulmonary embolism	Sudden onset: shortness of breath [at rest or on exertion], pleuritic chest pain [sudden, intense, sharp, stabbing or burning in nature, made worse by breathing/coughing/sneezing/laughing], cough +/- haemoptysis, tachypnoea, tachycardia, arrhythmia, cyanosis, hypotension
Intra-abdominal vein thrombosis (hepatic, splenic, mesenteric, renal)	Abdominal pain [may be out of proportion to physical exam findings], bloating, nausea, vomiting, diarrhoea, bloody stools, ascites, hepatomegaly if hepatic vein location
Ischemic stroke due to arterial thrombosis	Sudden onset of focal neurologic deficits such as difficulty with speech [dysphasia or dysarthria], hemiparesis, ataxic gait abnormal eye movements, facial paresis
Myocardial infarction due to coronary artery thrombosis	Chest pain [often crushing in nature], shortness of breath, arrhythmias, cyanosis, sudden death
Ischaemic limb, or aortic thrombosis	Cold pale limbs, loss of pulse
Adrenal glands (venous and typically secondary arterial occlusions)	Features of adrenal insufficiency (fatigue, dizziness, nausea, vomiting, diarrhoea)
Renal arteries/veins	Flank pain, abdominal pain, nausea, vomiting, haematuria, decreased urine output
Other unusual sites including retinal vein, optic artery	Reduced or blurred vision, floaters

additionally, at least two of the other five criteria must be satisfied. This is consistent with what has been termed pre-VITT. Confirmation of anti-PF4 antibodies is required for Levels 1 and 2 of VITT [51,54].

When all five VITT criteria are present, either a positive ELISA or functional anti-PF4 dependent antibody assay result is sufficient for Level 1 diagnostic certainty for VITT to be met (Table 6). Level 1 VITT can also be met where only three of the four VITT criteria related to thrombocytopenia, thrombosis, characteristic interval from vaccination to onset of illness and D-dimer are present, when a positive functional anti-PF4 dependent antibody assay is present.

Markedly elevated D-dimer (>4000 ng/mL) is one of the five VITT criteria and is needed to meet Level 1 in the absence of a positive functional anti-PF4 dependent antibody assay provided there is a positive anti-PF4 ELISA assay result. It is possible to meet Levels 2 and 3 of diagnostic certainty for VITT without a D-dimer measurement or with levels $\leq$ 4000 ng/mL ($\leq$ 8 times the ULN).

The TTS case definition is much less specific than VITT and as such has only 2 distinct levels of certainty. The main reason to have a case definition for TTS is to enable capture of forms of thrombosis and thrombocytopenia other than VITT induced by vaccination, as well as to capture possible VITT cases in settings with limited healthcare resources where anti-PF4 antibodies and possibly D-dimer levels cannot be measured. TTS level 1 and 2 both require demonstrated thrombocytopenia using the same expanded criteria as used for VITT. For Level 1 TTS the thrombosis or thromboembolism must be confirmed surgically, pathologically or by imaging OR the criteria for pre-VITT must be met: severe persistent headache with an onset from 5 to 30 days after vaccination with D-dimer > 8 times the upper normal limit (UNL) in the testing laboratory. Level 2 TTS needs presenting signs or symptoms that

Table 6
Criteria for vaccine-induced immune thrombocytopenia and thrombosis (VITT).

Condition	Defined criterion
A. Thrombocytopenia	Platelet count that meets $\geq$ 1 of the following: $<150 \times 10^9$/L Below the local laboratory lower limit for normal $\geq$50 % decrease from a previously documented count
B. Elevated D-dimer	A peak D-dimer that is > 8 times the upper normal limit for the testing laboratory (corresponding to > 4000 ng/mL (FEU) D-dimer*)
C. Acute or newly diagnosed thrombosis or thromboembolism	$\geq$1 of the following: Thrombotic event confirmed by pathology, imaging or surgical procedure (equals level 1 of the Brighton Collaboration thrombosis and thromboembolism case definition) Severe, persistent headache with onset from 5 to 30 days after vaccination[1]
D. Characteristic interval from vaccination to onset	Symptom onset must fall within 1 of the following intervals: Day 4 to day 30 after vaccination[2] Day 4 to day 42 after vaccination[2] IF the thrombotic event is an isolated DVT or pulmonary embolism
E. Anti-PF4 antibody	$\geq$1 of the following: Positive anti-PF4 antibody ELISA test Positive functional assay for PF4 dependent antibodies.

[1] Headache and other symptoms occurring in the first days following vaccination are common and rarely have any long-term significance.
[2] Date of vaccination defined as day 0.
* A normal D-dimer level effectively rules out VITT.

Table 7
Case definition and levels of diagnostic certainty for vaccine-induced immune thrombocytopenia and thrombosis (VITT).

Level 1 (definite case)	
1.1	**Presence of all five VITT criteria*** **OR**
1.2	**A positive functional assay for PF4 dependent antibodies (with or without a positive ELISA test)** **AND**
1.3	**Presence of 3 of the other 4 VITT criteria***
Level 2 (probable case)	
2.1	**A positive PF4 antibody ELISA assay without a functional assay result for PF4 dependent antibodies** **AND**
2.2	**Presence of three of the other four VITT criteria*** **AND**
2.3	**A more plausible alternative explanation for illness not found**
Level 3 (possible case)	
3.1	**Presence of any three of the five VITT criteria*** **AND**
3.2	**A more plausible alternative explanation for illness not found**

**1. thrombocytopenia, 2. elevated D-dimer, 3. acute or newly diagnosed thrombosis or thromboembolism, 4. characteristic interval from vaccination to onset, 5. anti-PF4 antibody (see Table 6 for definitions)*

are consistent with thrombosis or thromboembolism.

5.3. Rationale for including interval from vaccination to onset for both VITT and TTS case definitions

VITT represents a specific proven vaccine-induced adverse event and thus the case definition includes a criterion that defines the interval following vaccination to symptom onset [9–11,14–16,19]: specifically onset from 4 to 30 days following vaccination (day of vaccination is day

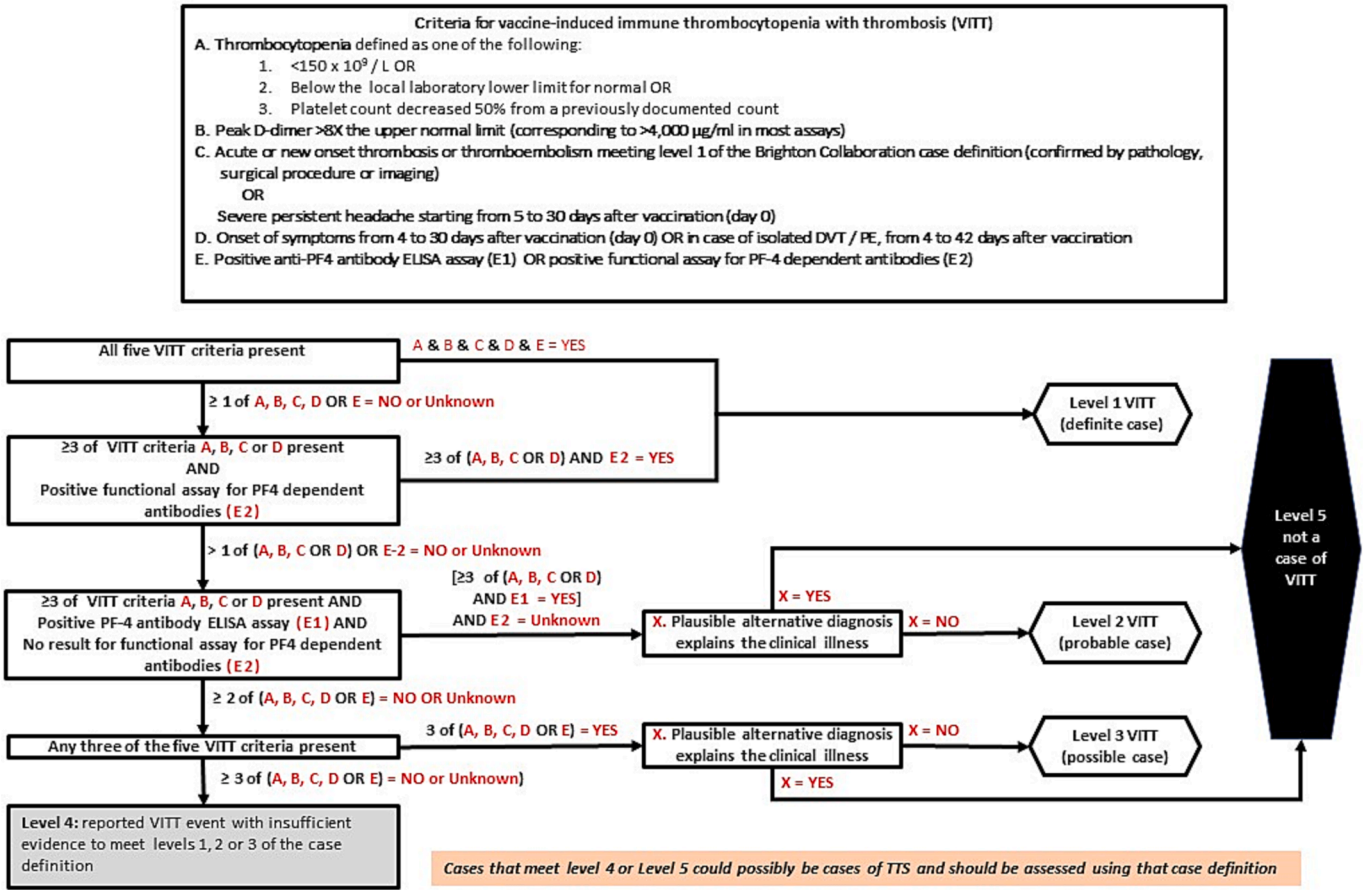

Fig. 3. Algorithm for vaccine-induced immune thrombocytopenia and thrombosis levels of certainty.

0) unless the thrombotic event is isolated deep vein thrombosis or pulmonary embolism, in which case the interval is extended to 42 days, as thrombosis at these sites may take longer to manifest [20,25]. The 42-day extended interval for cases of DVT or pulmonary embolism is consistent with that adopted by the UK and Australian Expert Haematology Groups [25,79,80]. Most definitions have used five days post-vaccination as the lower bound of the interval for consideration of VITT. However, one recent systematic review reported rare proven cases as early as 4 days following vaccination which was consistent with the professional experience of the expert haematologists in the Working Group [50].

The same interval from vaccination to symptom onset is required to meet either Level 1 or 2 of certainty for TTS. The rationale for this is that the TTS case definition is provided for low resource settings that cannot apply the more specific VITT case definition. This can also be true in high-income countries where some post-marketing spontaneous reports may be incomplete, precluding VITT ascertainment. It is assumed that the TTS case definition would be used for suspected VITT cases and thus the same interval following vaccination would be appropriate. In addition, given the many causes of thrombocytopenia with thrombosis, leaving out the upper time limit from vaccine to onset criterion would result in inclusion of many cases that may have occurred coincidental to vaccination. In situations where the interval is unknown, the separate case definitions for thrombocytopenia with thrombosis or thromboembolism could be used.

5.4. Rationale for exclusion criteria

Alternative diagnoses, including the immune-mediated and non-immune-mediated causes of TTS shown in Table 3, to explain the clinical illness has been included as a relative, exclusion criterion in both VITT and TTS case definitions, except for Level 1 diagnostic certainty for VITT. The Working Group agreed that given the specificity of requiring all five criteria, or 3 or 4 non-antibody criteria and the presence of functional PF4 antibodies, an alternative diagnosis would not have to be considered. Further description and diagnostic recommendations for the possible alternative diseases that can present with both thrombosis and thrombocytopenia are provided in the Supplementary Material. However, it is important to consider that patients can develop VITT in the presence of another illness that could also potentially explain the thrombocytopenia or thrombosis, e.g., patients with cancer who are vaccinated against COVID-19 could, additionally, develop TTS or VITT.

5.5. Considerations for settings with limited healthcare resources

While TTS and VITT occur in low- and middle-income countries (LMICs), most guidelines in the diagnosis and management of these conditions are difficult to use in these settings. Most of the tests needed to meet the case definition of VITT are not only difficult to perform, they are also frequently impracticable in settings with limited infrastructure. For example, in most regions of sub-Saharan Africa D-dimer testing will not be available. Therefore, the geographical distribution of VITT will appear heterogeneous, with many more cases being reported in higher-income countries than in LMICs. In low-resource settings, suspicion of TTS or VITT can be supported by typical findings from a peripheral blood smear demonstrating increased *in-vivo* platelet activation, i.e., heterogeneous platelet sizes and small platelet aggregates [20,81].

In contrast, the TTS case definition criteria are applicable in LMICs. Diagnosis is based on clinical assessment and judgment and thus TTS can be diagnosed in most settings. Healthcare workers should be trained to recognise the clinical symptoms and understand the need to determine platelet counts in case of signs of new thrombosis starting four days after

vaccination or severe persisting headache starting from 5 to 30 days after vaccination are of major importance for recognition of TTS and VITT in LMICs. Vaccination teams and staff working in emergency departments should be included in the education and training initiatives.

6. Thrombocytopenia with thrombosis syndrome (TTS) case definition

The case definition of TTS should be reserved for situations where VITT is suspected but criteria are not fulfilled, or tests are unavailable. Only two levels of certainty are included in the case definition (Table 4; Fig. 2). As specified, the TTS case definition identifies suspected VITT but may include the other immune-mediated causes of TTS and other, not yet well-characterised adverse vaccination effects (Table 3).

The criterion specifying the interval from vaccination to illness onset must be met for either Level 1 or Level 2 of certainty. The presence of a more plausible alternative explanation for the illness is an exclusion criterion for both Levels 1 and 2 of certainty for TTS. The alternative causes for TTS are the non-immune mediated conditions listed in Table 3.

7. Vaccine-induced immune thrombocytopenia and thrombosis case definition

There is no single criterion considered absolutely essential for all levels of diagnostic certainty for VITT. In up to 5 % of presenting cases, the platelet count can be normal and can fall below the normal range over days following presentation (Table 7; Fig. 3). If the diagnosis is made early and management is prompt, thrombosis may not be present. Anti-PF4 antibodies may not be detected in up to 3 % of cases, as ELISAs vary in their sensitivities to different antibodies. However, a more plausible alternative diagnosis that explains the clinical illness would exclude a diagnosis of VITT for Levels 2 and 3 of certainty. However, since underlying illness and VITT could potentially be present at the same time, this should be carefully considered.

8. Guidelines for data collection, analysis and presentation of VITT or TTS as an adverse event

Brighton Collaboration guidelines for data collection, analysis and presentation of safety data have been published previously for both pre- and post-licensure clinical studies and surveillance systems [82,83]. Both guidelines provide a sample adverse event report form and are in accordance with general drug safety guidelines by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the adverse event reporting form developed by the Council for International Organizations of Medical Sciences (CIOMS).

The focus of this section is to provide recommendations that are specific to TTS and VITT in a vaccine safety context with a goal to facilitate comparability of such data.

8.1. Data collection

8.1.1. Basis for thrombocytopenia

The criteria for thrombocytopenia, for both TTS and VITT, can be satisfied in three ways: an absolute platelet count $< 150 \times 10^9$ /L; a count that falls below the local laboratory lower limit of normal (LLN), when this is different from 150×10^9 /L; or a 50 % or more reduction from a known baseline count. The method used should be specified and the value of the local laboratory LLN should be specified, if used. When a known baseline count is used, the timing of the baseline measurement relevant to illness onset should be specified. When there are multiple platelet counts, the lowest value during the illness should be used.

8.1.2. D-dimer testing

If the D-dimer results are reported as a multiple of the local laboratory ULN, the value of the ULN used should be specified. Alternatively, the D-dimer results can be expressed in ng/mL (FEU). When there are multiple D-dimer results, the highest value during the illness should be used.

8.1.3. Interval from vaccination to onset of illness

The day of vaccination should be defined as day 0 when calculating the interval, in days, from vaccination to illness onset.

8.1.4. Alternative diagnoses for clinical illness

The presence of an alternative diagnosis is a criterion that makes meeting the case definition for both TTS and VITT less likely. In vaccine research settings, investigation for alternative diagnoses should be conducted whenever possible and documented for any cases classified as excluded (Supplementary Material, Tables 4 and 5). In low resource settings it is understood that extensive investigation for alternative diagnoses may be impossible. Nevertheless, clinical history and physical examination findings that may be relevant for an alternative diagnosis, should be noted (e.g., history of cancer, atrial fibrillation, liver disease, alcohol abuse, recent trauma or pregnancy) along with any investigations that were done to rule out alternative causes.

8.2. Data analysis

8.2.1. Case classification

Each case of VITT should be classified in one of five categories as follows:

- meets the case definition with one of the following levels of certainty:
  - Level 1
  - Level 2
  - Level 3
- does not meet the case definition:
  - Level 4: due to insufficient information to meet Levels 1, 2 or 3 of certainty
  - Level 5: not a case of VITT; an alternative diagnosis for the clinical illness identified.

The same classification scheme should be used for TTS, with the caveat that there are only 2 levels of certainty, not 3. The cases that do not meet the case definition should still be classified as Level 4 or Level 5, as defined above, because these levels apply across all Brighton case definitions regardless of how many levels of certainty there are that meet the case definition.

8.2.2. Interval from vaccination to illness onset

Cases should also be classified according to the time from vaccination (day 0) to illness onset. The Working Group recommends that the following intervals be used. Note that some of the intervals fall outside the recommended vaccine to onset interval, which is appropriate, since the classification will include cases that do not meet the case definition.

- 0 – <4 days after vaccination
- 4 – 14 days after vaccination
- 15 – 30 days after vaccination
- 31 – 42 days after vaccination
- >42 days after vaccination

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members of the working group. They do not necessarily represent the official positions of each author's organisation (e.g., government, university, or corporation).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.01.045.

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