Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19)

World Health Organization

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Abbreviations and acronyms

Ad26.COV2-S vaccine	Johnson & Johnson COVID-19 Ad26.COV2-S vaccine
AEFI	Adverse event following immunization
aHIT	Autoimmune heparin-induced thrombocytopenia
APTT	Activated partial thromboplastin time
BC	Brighton Collaboration
CDC	US Centers for Disease Control and Prevention
ChAdOx-1 vaccine	AstraZeneca COVID-19 ChAdOx-1 vaccine
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CT scan	Computerized tomography scan
CTPA	CT pulmonary angiogram
CVST	Cerebral venous sinus thrombosis
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EDTA	Ethylenediamine tetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EtD	Evidence-to-decision-making
FEU	Fibrinogen Equivalent Units
GACVS	Global Advisory Committee on Vaccine Safety
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation (a method of assessing the certainty of evidence)
HZ	Hazard ratio
HIT	Heparin induced thrombocytopenia
IgG	Immunoglobulin G
IRR	Incidence rate ratio
ITP	Idiopathic thrombocytopenic purpura
IVB	Immunizations, Vaccines and Biologicals Department
IVIG	Intravenous immunoglobulin
J&J	Johnson & Johnson
LMICs	Low and middle-income countries
MRI	Magnetic resonance imaging
MSD	Mental Health and Substance Use Department
NCD	Noncommunicable Diseases Department
NHAC	Non-heparin-based anticoagulants
OR	Odds ratio
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PF4	Platelet factor 4
PICO	Patient/intervention/comparator/outcome
PT	Prothrombin time

QNS	Quality Norms and Standards
RD	Risk difference
RPQ	Regulation and Prequalification
RR	Relative risk
SAGE	Strategic Advisory Group of Experts on Immunization
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SMR	Standardized morbidity ratio
SVT	Splanchnic vein thrombosis
TTP	Thrombotic thrombocytopenic purpura
TTS	Thrombosis with thrombocytopenia syndrome
VKA	Vitamin K antagonists
VIPIT	Vaccine-induced prothrombotic immune thrombocytopenia
VITT	Vaccine-induced thrombosis with thrombocytopenia
WHE	WHO Health Emergencies Programme
WHO	World Health Organization

Executive summary

Thrombosis with thrombocytopenia syndrome (TTS) is a rare adverse event that has been reported in individuals vaccinated coronavirus disease 2019 (COVID-19) non-replicating adenovirus vector-based vaccines (AstraZeneca COVID-19 ChAdOx-1 vaccine and Johnson & Johnson (J&J) Janssen COVID-19 Ad26.COV2-S vaccine). In patients with platelet activating anti-PF4 (PF4) antibodies this has been characterized as vaccine-induced immune thrombotic thrombocytopenia (VITT). In this update we present the latest data for the epidemiology, clinical presentation, clinical case management, treatment and pathophysiology of TTS. The present document provides guidance on the recognition and management of thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination.

The term **vaccine-induced immune thrombotic thrombocytopenia (VITT)** has been incorporated into the World Health Organization (WHO) classification of TTS. The term VITT should be used when platelet activating anti-PF4 antibodies have been detected, with a platelet function assay or enzyme-linked immunosorbent assay (ELISA), and no alternative diagnosis exists. This distinction is mostly relevant for epidemiological purposes at a population level, since the clinical case management of TTS patients should not differ from that of patients where the diagnosis cannot be confirmed either due to negative or pending results or absence of diagnostic resources.

Some patients may present with delayed-onset (at least 3 days) persistent headache with atypical features and warning signs, such as treatment resistance and progressive worsening headache, in the absence of cerebral thrombosis. This will be classified as **pre-VITT syndrome** if these patients present the rest of the typical features of VITT, which include reduced platelet count or in the lower end of the normal range, marked D-dimer increase and anti-PF4 antibodies. P**re-VITT syndrome** may represent an early stage of VITT, so prompt identification and early treatment may prevent development of a major thrombosis.

TTS, defined below, is broadly considered to be the presence of a thrombosis or thromboembolism, which presents more frequently in uncommon locations, such as the cerebral venous sinus, splanchnic veins or in multiple locations together with marked thrombocytopenia (<50 x 109 platelets /L) following vaccination with a COVID-19 non-replicating adenovirus vector-based vaccine. Cases of thrombosis or thromboembolisms in common locations, i.e., pulmonary, deep veins, coronary arteries, cerebral arteries have also been reported following vaccination with a COVID-19 non-replicating adenovirus vector-based vaccine. The case definition also requires the absence of a better alternative clinical explanation for the condition.

The cumulative incidence of TTS following vaccination with a non-replicating adenovirus vector-based vaccine ranges from 0.5 to 6.8 cases per 100 000 vaccinees. Incidence rates differ depending on the vaccine, age, sex, geographical distribution and interpretation of the case definition. The observed-to-expected rate is higher following vaccination with the ChAdOx-1 vaccine in females, in patients aged <60 years and following the first dose. Most TTS cases have been reported within 3 to 30 days following vaccination with a COVID-19 non-replicating adenovirus vector-based vaccine, although delayed presentation beyond 30 days has been reported. The most recent epidemiology suggests that the cumulative incidence of TTS is higher following the first dose of the COVID-19 vaccine than after subsequent doses. Information from low- and middle-income countries will be fundamental for understanding the incidence of TTS better, given that the adenovirus vector-based vaccines have been used more extensively in these countries.

The main risk factors for TTS following vaccination with COVID-19 adenovirus vector-based vaccines are the receipt of non-replicating adenovirus vector-based vaccines and younger age. There is currently no evidence that traditional risk factors for thrombosis or thromboembolisms, including pregnancy, increases the risk of TTS in this context.

Vaccine-induced thrombosis with thrombocytopenia (VITT) can be defined as a case of TTS, for which other causes have been excluded and the presence of anti-PF4 antibodies, detected using a reliable test. There are similarities between autoimmune heparin-induced thrombocytopenia (aHIT). TTS may be caused by the binding of anti-PF4 antibodies to platelets, causing platelet activation and aggregation,

thrombosis, platelet consumption and thrombocytopenia. However, the exact mechanisms are still unclear and are currently being investigated.

TTS should be suspected in patients presenting with severe, persistent, or unusual headache (when the patient has a prior history of headache), blurred vision, focal weakness or numbness, persistent abdominal pain with or without vomiting, sudden onset of breathing difficulty, chest pain or limb swelling or pains, unusual skin bruising and/or petechiae (tiny purple, red, or brown spots on the skin), usually within 3 to 30 days following vaccination. Patients with suggestive clinical symptoms should undergo investigations promptly to rule out thrombotic events and presence of thrombocytopenia.

Individuals who present with thrombosis shortly after vaccination, usually within 3 to 30 days) should be evaluated for thrombocytopenia, increased D-dimer and positive anti-PF4 antibodies. An enzyme-linked immunosorbent assay (ELISA) should be used to detect anti-PF4 antibodies, as rapid immunoassays can give false negatives. The presence of anti-PF4 antibodies in a patient with a thrombotic event and thrombocytopenia following COVID-19 vaccination confirms the diagnosis of VITT. Other biomarkers can be helpful in the laboratory diagnosis of TTS, including D-dimer, fibrinogen and blood smear to confirm reduced platelet numbers and to rule out platelet clumping. The case definition requires the absence of a better alternative diagnosis for the condition. Imaging examinations should be performed in patients with suspected TTS as soon as possible, depending on anatomical location, especially in those who present with thrombocytopenia within 30 days post-vaccination.

Vaccinated individuals should be advised to seek immediate medical attention if they develop symptoms described in the boxes above, particularly when they occur within 3 to 30 days after vaccination, although some cases have been reported later than 30 days post-vaccination. These patients should be investigated for thrombosis and thrombocytopenia, as described above. Reporting these symptoms must be made easy for the vaccine recipients and could include helplines, hospital vaccine centres, or online reporting systems. Any thrombosis in pregnant women within four weeks following vaccination should be considered ‘suspect’ and should be evaluated for TTS and other conditions associated with an increased risk of thrombosis.

Communication about COVID-19 vaccine safety and related events, including TTS, plays a key role in building and sustaining confidence and uptake of vaccination. Adequate planning and related activities should be in place to ensure that the necessary programme staff and stakeholders are well-informed prior to any event and to guide a timely, accurate and credible response where needed. More information on this area of work, including an adaptable job aid for health care workers,

Summary of WHO recommendations

- WHO recommends that all patients who present with TTS following COVID-19 vaccination should receive anti-coagulation (strong, very low certainty).
- WHO recommends that heparin may be used for anti-coagulation for individuals with TTS following COVID-19 vaccination (conditional, very low certainty). This is applicable to settings where NHACs are not available. Given the ongoing vaccination roll-out and the risk of TTS, countries should attempt to procure and make NHACs and IVIGs available.
- WHO recommends the use of intravenous immunoglobulins (IVIGs) or non-heparin-based anticoagulants (NHACs) for individuals with TTS following COVID-19 vaccination (strong, very low certainty).
- WHO recommends against the use of platelet transfusion for patients who present with TTS following COVID-19 vaccination in all cases other than emergency situations when surgery is strongly indicated, thrombocytopenia is severe (<50 x 109 platelets /L), and the patient is bleeding or platelet transfusion is required to be able to proceed with emergency surgery (strong, very low certainty).
- WHO does not provide any recommendation for steroid treatment as there was insufficient evidence to recommend the use or non-use of steroids but notes the general use of steroids and the likelihood that steroids will usually be given in combination with other treatments.

Chapter 1

Introduction

1.1 Background

Since March 2021, cases of thromboses associated with thrombocytopenia have been reported in patients vaccinated with the Oxford-AstraZeneca ChAdOx1-S and Johnson & Johnson (J&J) Ad26.COV2-S COVID-19 vaccines. Evaluation of the cases by national and international bodies concluded that there was a plausible causal link between these two non-replicating adenovirus vector-based vaccines and the thrombosis with thrombocytopenia events *(1-3)*.

This conclusion was based on the temporal association with vaccination, an increase in observed rates for cerebral venous sinus thrombosis (CVST) compared with expected baseline rates, the presence of simultaneous multiple thromboses in some patients, unusual sites and extent of thrombosis, the presence of thrombocytopenia and anti-platelet factor 4 (PF4) antibodies and a higher mortality rate than that the reported mortality rates in non-vaccinated patients with the same thrombosis *(1-30)*.

1.2 Rationale for the updated guidance

Since the initial publication of the interim guidance in July 2021, there has been extensive usage of the viral vector vaccines for the prevention of coronavirus disease 2019 (COVID-19) and the emergence of new evidence, especially for the use of heparin to treat in special clinical settings in low- and middle-income countries (LMICs). At the request of the Strategic Advisory Group of Experts on Immunization (SAGE) and the Global Advisory Committee on Vaccine Safety (GACVS) in October 2021, WHO decided to reconvene the expert group in 2022 to update the guidance. It was also decided to include additional sections on TTS management in pregnancy and breastfeeding, TTS management in children and public and patient-centred communication on TTS. The section on epidemiology was reviewed and updated. The terminology used, e.g., VITT and TTS was clarified and the clinical case classification process streamlined.

1.3 Aim of the updated guidance

Knowledge about TTS and VITT following vaccination with a COVID-19 adenovirus vector-based vaccine is rapidly evolving. This document aims to increase awareness about TTS in the context of COVID-19 vaccination and thereby help health care providers in the assessment and management of potential TTS cases. Individuals and health care providers must be aware of the symptoms of possible TTS to enable prompt diagnosis and early treatment. Healthcare providers should be aware of the relevant diagnostic tests and know which treatments should be used and which ones should be avoided. The existing data for the epidemiology, risk factors, aetiology, diagnosis and clinical management for TTS, with specific considerations for LMICs, were reviewed.

The aim of this document is to provide updated guidance on the recognition and clinical management of this rare adverse event, known as thrombosis with thrombocytopenia syndrome (TTS), following vaccination. This syndrome has received different names, including vaccine-induced immune thrombotic thrombocytopenia (VIITT), vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), and vaccine-induced thrombotic thrombocytopenia (VITT).

Chapter 2

Guideline development process and methods

2.1 Guideline Development Group

In April 2021 WHO's GACVS recommended the creation of a TTS Guideline Development Group (GDG) to address an urgent need for guidance on clinical case management of TTS. In October 2021, WHO decided to reconvene the expert group in 2022 to update the guidance, following a request from SAGE and GACVS. The GDG was composed of experts in internal medicine, epidemiology, haematology, immunology, neurology, neurosurgery and pharmacology. The selection of the experts ensured gender, age and geographic balance, including LMIC representation and WHO regional representation.

A WHO Steering Group provided support to the GDG for the development of this guidance. The Steering Group included representatives from the Immunizations, Vaccines and Biologicals (IVB), Quality Norms and Standards (QNS), Regulation and Prequalification (RPQ), Mental Health and Substance Use (MSD), Noncommunicable Diseases (NCDs) Departments and the WHO Health Emergencies Programme (WHE). The case definition was developed with input from a member of the Brighton Collaboration, who was also a member of the GDG. Several meetings were conducted to reach consensus on the case definition. As most publications were from high-income countries, most of the cases of TTS were from these countries. However, some cases were identified in VigiBase which includes data from countries who are members of the WHO Programme for International Drug Monitoring (PIDM), including some from LMICs

The members of the GDGs and the WHO Steering Group are listed in **Annex 1**. These 18 experts and a subject matter expert were all contracted by WHO, signed a confidentiality agreement and underwent a conflict of interest assessment. The work of the GDG was coordinated by the co-chair of the GACVS and the development of the treatment guidance section was overseen by a guideline methodologist. Both the interim guidance in 2021 and the updated guidance in 2022 were developed by four subgroups who worked independently worked independently on the key research questions (**Table 1**).

Table 1. Guideline Development Group: subgroups for interim and updated guidance

Subgroup	Interim guidance (2021)	Updated guidance 2022
1	Epidemiology, risk factors and pathophysiology	Epidemiology and prevention
2	Manifestation of TTS after COVID-19 vaccination	Clinical manifestations, diagnostic criteria, clinical case management, therapeutics and treatment and recommendations
3	Case definition, clinical features and laboratory diagnosis	Special groups: review and specific recommendations for pregnancy and breastfeeding, adolescents/children and other groups
4	Clinical case management, including review of drug treatment and other therapeutics	Communications aspects of TTS

2.2 Methodology for evidence to recommendations in the interim guidance – July 2021

Key questions were formulated by the GDG and the WHO Steering Group performed a literature search and identified studies were reviewed (see box below). These were then distributed to the GDG members for their comments and feedback which were collated in a zero draft by the subject matter expert. Extensive details of the methodological approaches used for development of the interim guidance, published

in July 2021 are given in the published interim guidance *(31)*. The interim guidance was developed between 27 April 2021 and 4 June 2021.

Box: Key questions

- What is the global aetiology, baseline epidemiology of TTS in adults post-COVID-19 vaccination?
- What is the clinical presentation of TTS in patients post-COVID-19 vaccination?
- Is an internationally agreed case definition for patients presenting with TTS post vaccination emerging in the literature? What definitions are currently available, including clinical features and laboratory diagnosis?
- What algorithm is most suitable for triaging and case management of patients with COVID-19 vaccine-related TTS and thrombosis or thromboembolism following vaccination with an adenovirus vector-based COVID-19 vaccine?
- The main component of the PICO question was population, because the clinical questions required a comprehensive literature search strategy.
- The second search strategy included the following terms: cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis (intra-abdominal), deep vein thrombosis (DVT), disseminated intravascular coagulation (DIC), pulmonary embolism (PE), stroke and myocardial infarction.

2.3 Methodology for evidence to recommendations in the updated guidance – June 2022

Since the publication of the initial interim guidance in July 2021, there has been extensive use of the viral vector COVID-19 vaccines and the emergence of new evidence, particularly about treatment modalities for the use of heparin in LMICs. It was also decided additional sections on TTS management in pregnancy and breastfeeding, TTS management in children and public and patient-centred communication about TTS were needed.

At the request of the SAGE and the GACVS, in October 2021, WHO decided to reconvene the TTS GDG to update the guidance. For this, the original GDG members were contacted and those who were willing to continue were included in the new GDG. Additional members were recruited, particularly to provide expertise for the new sections. All the GDG members were contracted by WHO, signed confidentiality agreements and underwent conflict of interest assessment. The GDG comprised 18 experts in internal medicine, epidemiology, haematology, immunology, neurology, neurosurgery and pharmacology who worked in subgroups (**Annex 1**). Membership of the GDG was controlled to ensure gender, age and geographic balance, as well as LMIC representation.

2.4 Timeline for the updated guidance

- July 2021: Interim TTS Guidance published;
- October 2021: Need for update communicated by SAGE and GACVS;
- November 2021: Identification and contact of experts; confidentiality undertakings signed; and declarations of interest and submitted and cleared;
- November 2021: Membership of subgroups defined, including for special populations;
- December 2021: Research questions developed and focus areas clearly defined by each subgroup;
- January 2022: Updated literature review, with support from the WHO Steering Group;
- February – March 2022: Zero draft harmonized and posted on dedicated SharePoint for feedback from all GDG members;

- April 2022: GRADE tables developed;
- June 2022: Discussions about evidence to recommendations;
- August 2022: Approved by Guideline Review Committee.

2.5 Literature search

A rapid systematic review of the literature based on the PICO questions formulated by the GDG was performed in May 2021 and repeated in October 2021. More details of the literature search can be found in **Annex 2**. For the 2022 updated guidance, the two clinical treatment questions were formulated using the PICO (population, intervention, comparator, outcome) framework as described below:

- **PICO 1:** Should heparin (**I**) compared with no heparin or other anticoagulants (**C**) be administered to patients diagnosed with TTS following COVID-19 vaccination (**P**)? The outcomes (**O**) are listed below.
- **PICO 2:** Should specific drugs or procedures* (**I**) versus none or other drugs or procedures (**C**) be administered to individuals who present with TTS following COVID-19 vaccination (**P**)? The outcomes (**O**) are listed below.

**IVIG, steroids, anticoagulants excl. heparin, thrombectomy, blood products transfusion, plasma exchange*

In the updated guidance, the population (**P**) included all individuals (adult men and women and children) who had received a COVID-19 vaccine with clinical signs and symptoms of thrombosis and associated novel thrombocytopenia within 4 to 28 days of vaccination. In this updated guidance, the following terms, without being associated with a new episode of thrombocytopenia were included: cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis (intra-abdominal), deep vein thrombosis (DVT), disseminated intravascular coagulation (DIC), pulmonary embolism (PE), stroke and myocardial infarction.

The GDG considered three outcomes (**O**) to be critical according to the GRADE approach, i.e., most important to the patients who will be affected by the recommendations:

1) recovery: defined as the explicit mention of discharge of the patient with a recovered status;
2) death: including all-cause death as well as treatment-specific and disease-specific deaths; and
3) intracranial haemorrhage: patients with an uncertain outcome were classified as neither recovered nor dead.

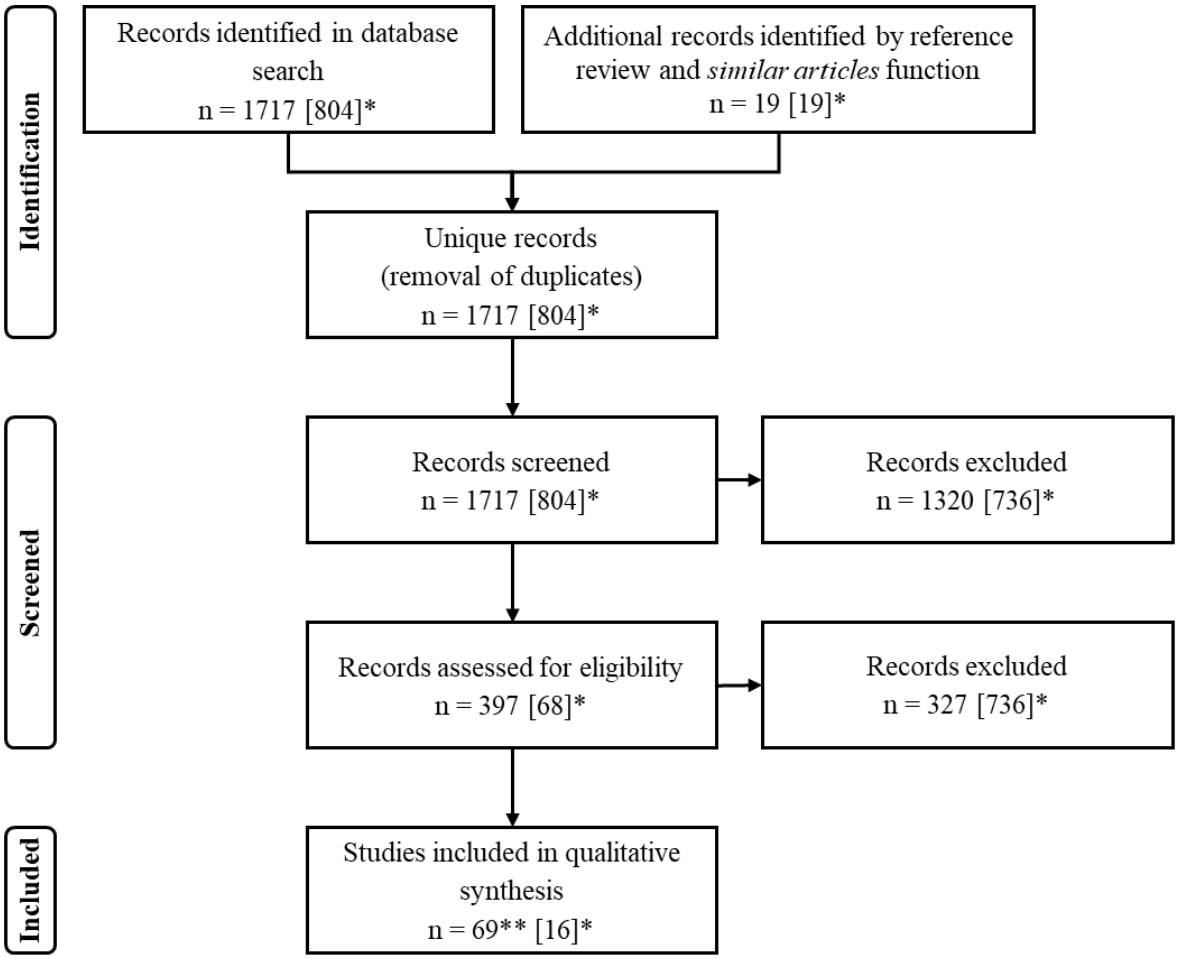
The revised review aimed to identify the existing evidence base on TTS in the context of COVID-19 disease and vaccination and to include evidence for pregnant women and children. The search strategies were developed by members of the WHO Steering Group and performed in three electronic databases: WHO COVID database, PubMed and the Global Index Medicus database. References lists in the identified publications were also scanned for pertinent publications and the 'similar articles' function in PubMed was used to identify additional publications. The screening was performed by the GDG subject matter expert, who reviewed the full text of all records and selected those that seemed relevant for the guidance update (**Fig 1**). These publications were classified in the various sections of the guidance draft zero and shared with the relevant GDG subgroup members. The members of each subgroup assessed the eligibility of the selected publications and incorporated relevant publications into the guidance. The updated background for TTS can be found in **Web Annex A**.

2.6 Quality assessment

The risk of bias in the treatment recommendations was assessed for each included study as described in the GRADE Handbook *(32)*. Risk of bias in each included study was assessed using the modified Newcastle-Ottawa scale. Specific biases of observational studies were analysed including failure to develop and apply appropriate selection of studies, presence of control populations, flawed measurement of both exposure and outcome, failure to adequately control confounding and incomplete follow-up. The data from the included studies were synthesized narratively and the certainty of evidence evaluated using GRADEPro guideline development tool *(33)*. The certainty of evidence assessment was based on the limitations in study design or execution, inconsistency of results, indirectness of evidence, imprecision and publication bias.

Fig 1. Flow diagram of identified, screened and included and excluded studies

2.7 Summary of findings



* numbers in square brackets correspond to studies identified for the interim guidance

** An additional manuscript in preparation was included: García-Azorín D, Balakrishnan M, Mitchell J, Takanashi F, Dua T, Pal S. Thrombosis with thrombocytopenia syndrome cases following non-replicant adenovirus vector-based vaccines from LMIC countries: a VigiBase analysis.

Methods

The literature search and review was updated to re-evaluate the effectiveness of therapies used for the treatment of patients with thrombosis with thrombocytopenia syndrome (TTS). Information from the interim draft was included in the present analysis.

Structure of PICO questions

The PICO questions were structured as:

Population: Patients diagnosed with TTS following COVID-19 vaccination.

Intervention: Treatment with NHACs, IVIGs, steroids, platelet transfusion or heparin.

Comparator: Patients not treated with the treatment of interest.

Outcome: recovery, death (all-cause) and intracranial haemorrhage.

Eligibility criteria

Studies providing information about patients with possible, probable or confirmed TTS, according to the WHO classification, who were treated with non-heparin-based anticoagulants (NHACs), intravenous immunoglobulins (IVIGs), steroids, platelet transfusions or heparin were eligible for inclusion.

Outcomes

The three outcomes were recovery, all-cause death and intracranial haemorrhage. For recovery, only cases that had fully recovered were considered and patients that were reported to still be hospitalized or admitted to an intensive care unit at the time of the publication were considered undetermined and not considered as 'recovered'.

Certainty of evidence

The overall certainty of the evidence for each outcome was classified as very low, low, moderate or high certainty. The following elements that could reduce the quality of the evidence were assessed, according to the GRADE handbook: limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision and publication bias. The following factors that could increase the quality of the evidence were evaluated: large effect size, all plausible confounding factors and dose-response gradient.

Risk of bias assessment was conducted to evaluate study limitations in the eligible observational studies and included failure to develop and apply appropriate eligibility criteria (inclusion of control population), flawed measurement of both exposure and outcome, failure to adequately control confounding and incompletely or inadequately short follow-up.

Statistical analysis

The methodology used in the interim guidance was used, with the addition of 95% confidence intervals and comparisons between groups.

First, the comparison treated vs non-treated, in which the percentages of patients who had each of the studied outcomes (recovery, death and intracranial haemorrhage) were compared between the patients who received the treatment being evaluated and the other patients that in the same studies who did not receive the treatment being evaluated. For each analysis, only studies that provided information specific for each drug were included. The 95% confidence intervals (CI) were also estimated. The results were presented together with the results from the first version, to facilitate their evaluation by the GDG members.

Second, the comparison treated vs all patients (including the treated patients) in which the percentages of patients who had each of the studied outcomes (recovery, death and intracranial haemorrhage) was compared between patients treated with each drug and those who were not treated with the drug in these studies.

2.8 External review

Anastasia Phillips and Alexis Pillsbury from the National Centre for Immunisation Research and Surveillance (NCIRS) in Australia reviewed the guidance. Both experts signed a confidentiality agreement and were assessed for any conflict of interest.

2.8 Limitations

The main limitations of the present guidance are related to the quality and quantity of the existing evidence, which is often based on single cases or case series. The degree of certainty was affected by the presence of biases that should be better managed in future studies. In addition, the number of patients represented in the analysis of the different treatment modalities was not balanced and in some cases was particularly low. Evidence regarding some treatment options for LMIC settings was also limited and should be properly evaluated, ideally with well-designed observational studies or with randomized controlled trials.

The GDG did not include patient representatives. Including patient representatives should be considered in future updates.

2.9 Evidence to decision-making for updated treatment guidance

Only studies with valid information for each of the outcomes were analysed in the review and any patients with incomplete information about the outcomes were not considered as recovered or dead. The outcome rates were calculated for all patients in the individual studies, regardless of treatment received and also only for patients who had received the treatment of interest. The outcome rates for all patients were calculated

by dividing the total number of patients with the outcome by the total number of patients included in each study. The outcome rates for each specific treatment were calculated by dividing the total of patients with the outcome of interest who received the treatment by the total number of patients who received the treatment in studies that reported valid data for the treatment. In the updated version, 95% confidence intervals (CI) were also estimated. Also, the percentages of patients who had each of the studied outcomes (recovery, death and intracranial haemorrhage) were compared between patients who received a given treatment and those who did not. The results were presented along with the results from the interim guidance, to facilitate evaluation by the GDG. The total number of studies with valid information for each of the different outcomes was described, as well as the total number of patients in each of the studies. Only the data available in the publications were analysed and no attempt to find missing data was made. Summary of findings (SoF) are presented in GRADE Evidence Profile Tables in **Web Annex B**.

2.9 Formulation of recommendation in the updated guidance based on evidence presented

A virtual meeting was held via Zoom on 6 June 2022. The meeting was chaired by a member of the GDG approved by the group. An experienced guideline methodologist facilitated the evidence-to-decision-making (EtD) process as described in the WHO Handbook for Guideline Development *(34)*. Although the original aim was to base all decisions on a consensus, at the beginning of the meeting the GDG members agreed that if any decisions required a vote, the vote would need to be carried by a majority of 60% of the votes.

The GDG reviewed the evidence contained in the systematic reviews and in the GRADE Evidence Profile Tables and discussed the topics under consideration, facilitated by the guideline methodologist. The GRADE EtD communicate the GDG's judgements about several factors as well as their judgements on the benefits and harms and their certainty. These factors include:

- the values and preferences of end-users;
- resource use, including costs and cost-effectiveness;
- potential impact on human rights and equity; and
- acceptability and feasibility.

No additional studies were commissioned to inform the factors above and the GDG were asked to consider judgments regarding variability and uncertainty for each factor from their own knowledge, expertise, experience and observations in the field.

During the virtual meeting, care was taken to ensure that all members of the GDG gave their responses through regular unofficial votes and use of the chat function to obtain the GDG members' views on the direction of each recommendation, i.e., for or against an intervention and on the strength of each recommendation, i.e., strong or conditional. The methodologist also asked participants to raise their hands to show support for each separate option. Although there was no formal vote system, this approached enabled the methodologist and the chair to assess the distribution of opinions and to prompt further discussion with the aim of reaching consensus.

The strength of the recommendation was established by considering both the certainty of the evidence and the availability and feasibility of the interventions, as well as the values and preference of patients and their families, the acceptability to all stakeholders including clinical staff and the impact on equity. A recommendation **for** an intervention indicates that it should be implemented and a recommendation **against** an intervention indicates that it should not be implemented. The strength of a recommendation, which was either 'strong' or 'conditional', reflects the degree of confidence the GDG had that the desirable effects of the recommendation outweighed the undesirable effects, for a positive recommendation, or the inverse, that the undesirable effects outweighed the desirable effects, for a negative recommendation.

The final wording of each recommendation, including an indication of its direction and strength, was confirmed by consensus between all GDG members and each member of the GDG was asked to express

their decision verbally. The judgements made by the GDG related to each recommendation are summarized in **Table 2**.

Table 2: Summary of GDG judgements related to recommendations

PICO 1: Should heparin (I) compared with no heparin or other anticoagulants (C) be administered to individuals diagnosed with TTS following COVID-19 vaccination (P)?	
Question	**GDG judgement on 6 June 2022**
1. Is the problem a priority?	Yes
2. How substantial are the benefits?	GDG judgment was diverse – from uncertain to large
3. How substantial are the harms?	Small, trivial, uncertain
4. What is the overall certainty of the evidence?	Very low
5. What is the balance between benefits and harms?	Probably favours heparin, uncertain
6. How do patients and their families value heparin for TTS?	Important: uncertainty or variability, Possibly important: uncertainty or variability, Probably not important: uncertainty or variability Not important: uncertainty or variability
7. How large are the resource requirements (costs)?	Large savings, depends on other available treatments and context
8. What is the certainty of the evidence for the costs?	No data available, no judgment made
9. Is heparin cost-effective?	Likely to favour heparin, varied
10. What would the impact be on health equity?	Increased, probably increased
11. Is heparin acceptable to all stakeholders?	Yes, probably yes
12. Is heparin feasible to implement?	Yes

Concluding recommendation by the GDG on the use of heparin to treat patients with TTS on 6 June 2022:
• Does the GDG wish to make a recommendation, is there enough evidence?
  ○ Yes
• Is the recommendation in favour or against heparin for TTS?
  ○ In favour
• Is the recommendation strong or conditional?
  ○ Conditional (context specific if non-heparin-based anticoagulants are not available)	

PICO 2: Should specific drugs or procedures* (I) versus none or other drugs or procedures (C) be administered to individuals who present with TTS following COVID-19 vaccination (P)?	
Question	**GDG judgement on 6 June 2022**
1. Is the problem a priority?	Yes
2A. How substantial are the benefits for IVIG?	Large
2B. How substantial are the benefits for steroids?	Moderate, small, uncertain
2C. How substantial are the benefits for platelet transfusion?	No benefit, uncertain
2D. How substantial are the benefits for non-heparin anti-coagulants?	Large
3A. How substantial are the harms for IVIG?	Uncertain – potential for selection bias and potential for harm
3B. How substantial are the harms for steroids?	Uncertain
3C. How substantial are the harms for platelet transfusion?	Large, uncertain (should be withheld unless there is an active bleeding or platelet transfusion is needed to proceed with emergency surgery)
3D. How substantial are the harms for non-heparin anti-coagulants?	Small, trivial
4. What is the overall certainty of the evidence?	Very low
5A. What is the balance between benefits and harms for IVIG?	Favours intervention, probably favours intervention
5B. What is the balance between benefits and harms for steroids?	Does not favour either, probably favours no intervention, uncertain
5C. What is the balance between benefits and harms for platelet transfusion?	Favours no intervention
5D. What is the balance between benefits and harms for non-heparin anti-coagulants?	Favours intervention

PICO 2: Should specific drugs or procedures* (I) versus none or other drugs or procedures (C) be administered to individuals who present with TTS following COVID-19 vaccination (P)?	
Question	**GDG judgement on 6 June 2022**
6. How do people value treatment for TTS?	Important uncertainty or variability, no important uncertainty or variability (question is hypothetical – patients don't have a choice – for platelets we have better evidence currently – there is less uncertainty or variability for treatment modalities now and patients would want treatments.)
7. How large are the resource requirements (costs)?	Varies
8. What is the certainty of the evidence for the costs?	No data so no judgment made
9. Are treatments for TTS cost-effective?	Favours treatment
10. What would the impact be on health equity?	Increased (this is irrespective of the cost. Government should provide treatment; will increase equity and if recommended govts will allocate resources)
11. Are treatments for TTS acceptable to all stakeholders?	Yes, probably yes
12. Are treatments for TTS feasible to implement?	Yes, probably yes
*IVIG, steroids, anticoagulants excl. heparin, thrombectomy, blood products transfusion, plasma exchange	
Concluding recommendation by the GDG for non-heparin-based interventions to treat patients with TTS on 6 June 2022:	

	IVIG	**NHAC**	**Platelet transfusion**	**Steroids**
1. Recommendation?	Yes	Yes	Yes	No recommendation
2. In favour or against?	In favour	In favour	Against	
3. Strong or conditional	Strong	Strong	Strong with caveats	

Chapter 3

Treatment recommendations and rationale

1. All patients who present with TTS following vaccination with a COVID-19 vaccine should receive anti-coagulation treatment (*strong, very low certainty)*

Result of the literature review

The GDG noted that anti-coagulant treatment is necessary for thrombotic conditions such as TTS. A total of 42 studies including 495 patients with TTS that assessed different anti-coagulant therapies were considered. The outcome recovery was more frequently observed in patients treated with NHACs than in those not treated with NHACs and the outcomes, intracranial haemorrhage and death, were less frequently observed in patients treated with NHACs.

Certainty of the evidence

The overall certainty of the evidence was judged as very low as the evidence came from observational studies. Risk of bias was judged as serious, inconsistency and indirectness were also judged as serious but imprecision was judged as not serious.

Rationale

The GDG agreed that the evidence supported the benefits from administration of NHACs likely being large and the harms from them being likely being limited. Taken together and acknowledging the overall very low certainty of evidence, the GDG determined that the balance between benefits and harms favoured the use of NHACs for the treatment of TTS.

Some members of the GDG thought that there was likely to be important uncertainty or variability among patients about their values and preferences whereas others thought that as patients would not have the choice in life-threatening circumstances, there would be less uncertainty or variability for their values and preferences about the treatment modalities and they would want the treatments. The cost and resources required to provide NHACs would vary across regions and countries with members describing NHAC as expensive. However, it was acknowledged that governments may be able to reduce costs of treatments, especially during vaccine roll out, in order to ensure appropriate treatment for TTS following immunization would be available. The GDG argued that if lives were saved, the interventions were likely to be cost-effective although no data were available. Equity would be increased if these interventions were made available everywhere, irrespective of cost. All members of the GDG felt that NHACs were acceptable and feasible to implement.

Given the life-saving potential of NHAC and the limited harms observed in the studies, the GDG agreed to make a strong recommendation in favour of NHACs, despite the low certainty evidence. The GDG noted that the quality of the evidence is unlikely to improve, since TTS is a rare condition that requires urgent treatment, implying that conducting randomized controlled trials would be challenging.

2. Heparin may be used for anti-coagulation in patients with TTS following vaccination with a COVID-19 vaccine (conditional, very low certainty)

REMARK: This is applicable to settings were NHACs are not available; given the ongoing COVID-19 vaccine roll-out and the risk of TTS, countries should attempt to procure and make NHACs and IVIGs available.

Result of the literature review

Heparin was assessed in 26 studies including 588 patients with TTS. There were 9 case reports and 17 case series. Recovery rates in patients treated with heparin were higher than in patients not treated with heparin

and patients treated with heparin had lower mortality rates. The rates of haemorrhage were higher in patients treated with heparin than in those not treated with heparin.

Certainty of the evidence

The overall certainty of the evidence was judged to be very low. The evidence came from observational studies. Risk of bias was judged to be serious, inconsistency, indirectness and imprecision were also judged to be serious. Publication bias was strongly suspected, because the publications were about patients with poor outcome and were mainly from high-income countries.

Rationale

The GDG were divided about the benefits of heparin with judgments ranging from uncertain to large. The harms were acknowledged to be uncertain also, with several GDG members noting that the data indicated harms may be limited. Taken together and acknowledging the overall very low certainty of evidence, some members of the GDG felt that the balance between benefits and harms probably favoured heparin whereas others felt it was uncertain.

The GDG noted that patients' values and preferences were likely to vary, depending on what other treatments were available. If no other anticoagulation treatment was available, most patients would prefer heparin. Provision of heparin could result in large savings but this would only be relevant in settings where other anticoagulants were not available. As heparin is cheaper than other anticoagulants, it was likely to be cost-effective but this would also depend on the setting. Equity would be enhanced with greater availability. The GDG felt that heparin treatment would be both feasible and acceptable to stakeholders.

The GDG agreed to make a conditional recommendation in favour of heparin but felt that caveats needed to be specified and clarified. These were that the decision to use heparin for the treatment of TTS should be based on the non-availability of other anticoagulants and monitoring of treated patients during implementation should be emphasized. These caveats are shown in the remarks following the recommendation above.

3. IVIGs should be used for treating individuals with TTS following vaccination with a COVID-19 vaccine (strong, very low certainty)

Result of the literature review

A total of 43 studies including 278 patients treated with IVIGs were included. Recovery rates were higher in patients treated with IVIG than in those not treated with IVIGs. Death rates were lower in patients treated with IVIGs and haemorrhage rates were higher among patients treated with IVIGs than in those not treated with IVIGs.

Certainty of the evidence

The overall certainty of the evidence was judged to be very low. Evidence came from observational studies. Risk of bias, inconsistency, indirectness and imprecision were all judged to be serious. Publication bias was strongly suspected because the publications were about patients with poor outcome and were mainly from high-income countries.

Rationale

The GDG agreed that the evidence supported that the benefits from administration of IVIGs likely being large and the harms from them being likely being limited. There was uncertainty about the extent of the harms from IVIGs as there was the potential for patient selection bias to be present in the studies, with more severely ill patients receiving IVIGs. Taken together and acknowledging the overall very low certainty of evidence, the GDG determined that the balance between benefits and harms probably favoured the use of IVIGs for treating TTS.

Some members of the GDG felt that there was likely to be important uncertainty or variability among patients for their values and preferences, whereas others felt that as patients would not have a choice in life-threatening circumstances, there would be less uncertainty or variability about treatment modalities and patients would want the treatments. The cost and resources required to provide IVIGs would vary across regions and countries with members describing IVIGs as being expensive and the necessary facilities and human resources required as being also expensive. However, it was acknowledged that governments may be able to reduce costs of treatments, especially during vaccine roll out, in order to ensure appropriate treatment for TTS following CVOID-19 immunization. The GDG agreed that if lives were saved, the interventions were likely to be cost-effective, although no data were available. Equity would be increased if these interventions were made available, irrespective of cost. All members of the GDG felt that IVIG treatment was acceptable and feasible to implement.

Given the benefits of IVIG treatment and the limited harms observed in the studies, the GDG agreed to make a strong recommendation in favour of IVIGs. The GDG members stated that having higher quality of evidence would be challenging and the treatment outcomes from IVIG treatment outweighed any undesirable effects.

4. Platelet transfusion should not be used for treatment of patients with TTS following vaccination with a COVID-19 vaccine, except in emergency situations where surgery is strongly indicated, thrombocytopenia is severe and platelet transfusion is required (strong, very low certainty)

Result of the literature review

Fourteen studies provided information about platelet transfusion, accounting for 169 patients. Recovery rate was lower in patients treated with platelet transfusion than in patients not treated with platelet transfusion. Death rate and haemorrhage rate were higher in patients treated with platelet transfusion than in patients not treated with platelet transfusion.

Certainty of the evidence

The overall certainty of the evidence was judged as very low. Evidence came from observational studies. Risk of bias was judged as serious, inconsistency and indirectness were also judged as serious, while imprecision was judged as not serious. Publication bias was strongly suspected because the publications were about patients with poor outcome and were mainly from high-income countries.

Rationale

The GDG noted that there were no benefits for platelet transfusion and that harms were large although the data were uncertain. The GDG all agreed that the balance between benefit and harms did not favour platelet transfusion for the treatment of TTS.

The GDG noted that there was likely to be no uncertainty about the patients' values and preference and that they would not wish to receive platelets given the recorded harms. The other GRADE domains were not discussed given the evidence of harms which was judged sufficient to make a recommendation.

Given the large harms, the GDG made a strong recommendation against platelet transfusion in all cases of TTS, except in emergency situations where surgery would be strongly indicated, with severe thrombocytopenia ($<50 \times 10^9$ platelets /L), and bleeding or if platelet transfusion is required to be able to proceed with emergency surgery.

5. KEY CONSIDERATION: The GDG did not provide any recommendation on steroid treatment but noted the general use of steroids and the likelihood that steroids would usually be given in combination with other treatments

Result of the literature review

Twenty-five studies including 224 patients reported data on steroids in the treatment of TTS. The recovery rate in patients treated with steroids was slightly higher than in those not treated with steroids. Death rate and haemorrhage rate were also higher in patients treated with steroids than in those not treated with steroids.

Certainty of the evidence

The overall certainty of the evidence was judged as very low. Evidence came from observational studies. Risk of bias was judged as serious, inconsistency, indirectness and imprecision were judged as serious. Publication bias was strongly suspected.

Rationale

The GDG noted that the data were uncertain and the GGD judged the benefits of steroids for TTS to be small or moderate. The harms were judged to be uncertain. The GDG judged the balance between benefits and harms to be uncertain with some members noting that there may be no directional effect and others noting the balance was probably against the administration of steroids.

Some GDG members noted that there was likely to be important variability and uncertainty for the patients' values and preferences whereas others felt that it would not be an issue given the hypothetical nature of the question when patients are in an emergency situation. The use of steroids in combination with other modalities resulted in the GDG having difficulties to judge the other GRADE domains but noted that steroids are acceptable, affordable, feasible and available and would, therefore, be likely to increase equity. There was a biological plausibility for the use of steroids but indirect evidence favoured their use, however, the lack of evidence of their use specifically for TTS resulted in the GDG making no recommendation.

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Annex 1 Contributors

Contributors to the guideline development process are listed in Tables A1.1 to A1.5.

Table A1.1 Members of the WHO Steering Group for the development of the guidelines on TTS

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Table A1.2 Members of the Guideline Development Group for TTS

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... continued

Name	Affiliation	Gender	Expertise
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* Members of GDG for interim guidance; **Members of GDGs for interim and updated guidance; ***Members of GDG for updated guidance

[a]Pioneered the development of the WHO classification of TTS based on the degree of certainty.

Four subgroups of experts were constituted.

- **Subgroup 1:** Epidemiology and prevention (including recommendations on prevention of TTS if applicable) – Huyen Tran, Riitta Lassila, Georgy Genov, Narendra Arora, DS Akram, Alla Guekht and Joseph Mitchell. They were supported by the WHO Steering Group including Annick Janin.

- **Subgroup 2:** Clinical manifestations, diagnostic criteria, clinical case management, therapeutics and treatment and recommendations – Kameshwar Prasad, Mike Gold, Kiran Takur, Imo Akpan, Huyen Tran, Prasanna Kumar, Dale Nordenberg, Georgy Genov, Andreas Greinacher, Claudia Gonzalez, Tom Solomon and Agustina Chairway-Felli. They were supported by the WHO Steering Group including Nicoline Schiess and Adwoa Bentsi Enchill
- **Subgroup 3:** Special groups: review and specific recommendations for pregnancy and breastfeeding, adolescents/children and other groups: Ushma Mehta, Chahnez Charfi Triki, Denise J. Jamieson, Suzie Marie Gomes. They were supported by the WHO Steering Group including Noha Iessa and Sonia Chabane
- **Subgroup 4:** Communications aspects of TTS for various stakeholders included Madhava Ram Balakrishnan and Eun Mi Kim (WHO). The work was coordinated by Lisa Menning (WHO),

Table A1.3 Technical advisers for the development of the guidelines for TTS

Name	Affiliation	Role
David Garcia Azorin	Hospital Clínico Universitario de Valladolid, Valladolid, Spain	Subject matter expert
Nandi Siegfried	Medical Research Council of South Africa, Faculty of Health Sciences, University of Cape Town Cape Town, South Africa	Evidence Review Team lead; consultant for development of the guidelines

Table A1.4 Evidence Review Team for TTS guidelines

Name	Affiliation	Role
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Jesus Lopez Alcalde	HQ/SCI Chief Scientist and Science Division	Data research
Lucy Turner	HQ/MST Methods	Data research

Table A1.5 External reviewers of the guidelines on TTS

Name	Affiliation	Expertise	Interests declared
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Name	Affiliation	Expertise	Interests declared
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*External reviewers for interim guidance; ** External reviewers for updated guidance.

Annex 2 Search strategies for bibliographic databases: PubMed, WHO COVID-19 Database and Global Index Medicus

Modifications to the search strategy for the updated guidance are indicated in red.

Population	Patients with vaccine-related TTS. Similar pathophysiology as that for heparin–-induced thrombocytopenia
Interventions	Non-heparin-based anticoagulant (NHAC)s, high-dose intravenous immunoglobulin (IVIG), and prednisolone, thromboprophylaxis, steroids, folate, platelet transfusion, splenectomy Platelet count <50 000/µL
Full PubMed search strategy	(("Heparin induced thrombocytopenia"[tiab] OR ((prothrombotic OR thrombosis[tiab] OR thrombotic[tiab] OR thromboembolism[tiab]) AND ("thrombocytopenia"[tiab] OR thrombocytopenic[tiab]))) AND systematic[sb]) (157)
	((prothrombotic OR thrombosis[tiab] OR thrombotic[tiab] OR thromboembolism[tiab]) AND ("thrombocytopenia"[tiab] OR thrombocytopenic[tiab])) AND (2020:2021[pdat]) AND (Coronavirus*[TIAB] OR corona?virus[Tiab] OR "Coronavirus"[Mesh] OR coronavirinae[tiab] OR coronaviridae[tiab] OR betacoronavirus[tiab] OR "corona pandemic"[tiab] OR COVID OR COVID-19[TW] OR NCov[Tiab] OR 2019ncov[TW] OR (SARS AND COV) OR SARS2 OR "CoV 2"[tiab] OR CoV2[tiab] OR "Coronavirus Infections"[Mesh] OR NCOV19[tiab] OR "solidarity trial"[tiab]) (142)
	OR "Vaccine Induced Thrombocytopenia Syndrome"[tiab] OR "vaccine-induced prothrombotic immune thrombocytopenia"[tiab] OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia"[tiab] OR " inflammatory and thrombotic response to vaccination"[tiab] OR "Rare thromboembolic syndrome"[tiab] OR VIPIT[tiab] OR ((("Cerebral venous sinus thrombosis"[tiab] OR " Cerebral venous thrombosis"[tiab] OR " Sinus Thrombosis, Intracranial"[tiab] OR "cerebral sinovenous thrombosis"[tiab] OR "cerebral vein thrombosis"[tiab] OR "cerebral venous and sinus thrombosis"[tiab] OR "cerebral vein and dural sinus thrombosis"[tiab] OR " cavernous sinus thrombosis"[tiab] OR CVST[tiab] OR "Anti PF4 antibodies") AND ("thrombocytopenia"[tiab] OR thrombocytopenic[tiab]))
Full String WHO COVID-19 Database	"Heparin induced thrombocytopenia" OR ((prothrombotic OR thrombosis OR thrombotic OR thromboembolism) AND ("thrombocytopenia" OR thrombocytopenic)) OR "Vaccine Induced Thrombocytopenia Syndrome" OR "vaccine-induced prothrombotic immune thrombocytopenia" OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia" OR " inflammatory and thrombotic response to vaccination" OR "Rare thromboembolic syndrome" OR VIPIT OR ((("Cerebral venous sinus thrombosis" OR " Cerebral venous thrombosis" OR " Sinus Thrombosis, Intracranial" OR "cerebral sinovenous thrombosis" OR "cerebral vein thrombosis" OR "cerebral venous and sinus thrombosis" OR "cerebral vein and dural sinus thrombosis" OR " cavernous sinus thrombosis" OR CVST OR "Anti PF4 antibodies") AND ("thrombocytopenia" OR thrombocytopenic))

WHO Database Link	https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/?output=site&lang=en&from=0&sort=&format=summary&count=20&fb=&page=1&skfp=&index=tw&q=%22Heparin+induced+thrombocytopenia%22+OR+%28%28prothrombotic+OR+thrombosis+OR+thrombotic+OR+thromboembolism%29++AND+%28%22thrombocytopenia%22+OR+thrombocytopenic%29%29+++OR+%22Vaccine+Induced+Thrombocytopenia+Syndrome%22+OR+%22vaccine-induced+prothrombotic+immune+thrombocytopenia%22+OR+%22Vaccine-Induced+Immune+Thrombotic+Thrombocytopenia%22+OR+%22+inflammatory+and+thrombotic+response+to+vaccination%22+OR+%22Rare+thromboembolic+syndrome%22+OR+VIPIT+OR++%28%28%22Cerebral+venous+sinus+thrombosis%22+OR+%22+Cerebral+venous+thrombosis%22+OR+%22+Sinus+Thrombosis%2C+Intracranial%22+OR+%22cerebral+sinovenous+thrombosis%22+OR+%22cerebral+vein+thrombosis%22+OR+%22cerebral+venous+and+sinus+thrombosis%22+OR+%22cerebral+vein+and+dural+sinus+thrombosis%22+OR+%22+cavernous+sinus+thrombosis%22+OR+CVST%29++AND+%28%22thrombocytopenia%22+OR+thrombocytopenic%29%29&search_form_submit=
Global Index Medicus	tw:("Heparin induced thrombocytopenia" OR ((prothrombotic OR thrombosis OR thrombotic) AND ("thrombocytopenia" OR thrombocytopenic)) OR "Vaccine Induced Thrombocytopenia Syndrome" OR "vaccine-induced prothrombotic immune thrombocytopenia" OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia" OR " inflammatory and thrombotic response to vaccination" OR "Rare thromboembolic syndrome" OR vipit OR (("Cerebral venous sinus thrombosis" OR " Cerebral venous thrombosis" OR " Sinus Thrombosis, Intracranial" OR "cerebral sinovenous thrombosis" OR "cerebral vein thrombosis" OR "cerebral venous and sinus thrombosis" OR "cerebral vein and dural sinus thrombosis" OR " cavernous sinus thrombosis" OR cvst) AND ("thrombocytopenia" OR thrombocytopenic))) AND (type_of_study:("guideline" OR "policy_brief" OR "systematic_reviews"))
GIM LINK	https://pesquisa.bvsalud.org/gim/?output=site&lang=en&from=0&sort=&format=summary&count=20&fb=&page=1&filter%5Btype_of_study%5D%5B%5D=guideline&filter%5Btype_of_study%5D%5B%5D=policy_brief&filter%5Btype_of_study%5D%5B%5D=systematic_reviews&index=tw&q=tw%3A%28%22Heparin+induced+thrombocytopenia%22+OR+%28%28prothrombotic+OR+thrombosis+OR+thrombotic%29++AND+%28%22thrombocytopenia%22+OR+thrombocytopenic%29%29+++OR+%22Vaccine+Induced+Thrombocytopenia+Syndrome%22+OR+%22vaccine-induced+prothrombotic+immune+thrombocytopenia%22+OR+%22Vaccine-Induced+Immune+Thrombotic+Thrombocytopenia%22+OR+%22+inflammatory+and+thrombotic+response+to+vaccination%22+OR+%22Rare+thromboembolic+syndrome%22+OR+vipit+OR++%28%28%22Cerebral+venous+sinus+thrombosis%22+OR+%22+Cerebral+venous+thrombosis%22+OR+%22+Sinus+Thrombosis%2C+Intracranial%22+OR+%22cerebral+sinovenous+thrombosis%22+OR+%22cerebral+vein+thrombosis%22+OR+%22cerebral+venous+and+sinus+thrombosis%22+OR+%22cerebral+vein+and+dural+sinus+thrombosis%22+OR+%22+cavernous+sinus+thrombosis%22+OR+cvst%29++AND+%28%22thrombocytopenia%22+OR+thrombocytopenic%29%29%29+AND+%28+type_of_study%3A%28%22guideline%22+OR+%22policy_brief%22+OR+%22systematic_reviews%22%29%29&search_form_submit=

Rapid Review Group	Research Topic Thrombosis with Thrombocytopenia Syndrome

WHO COVID-19 Database

https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/

Concept	Search string	Results 22.05.2021
#1- TTS in COVID-19	((prothrombotic OR thrombosis OR thrombotic OR thromboembolism OR embolism OR thrombus OR D-dimer OR "Splanchnic vein" OR SVT OR CVST OR DVT OR "Disseminated Intravascular coagulation" OR "consumptive coagulopathy" OR "disseminated intravascular coagulopathy" OR "defibrination syndrome" OR "defibrinogenation syndrome" OR "acquired afibrinogenemia" OR Stroke OR "cerebrovascular accident" OR "CVA" OR "cerebral infarct" OR "ischemic infarctions" OR "CNS infarction" OR "Myocardial Infarction" OR "coronary infarction") AND ("thrombocytopenia" OR thrombocytopenic OR "Anti PF4 antibodies" OR "platelet factor 4" OR "low platelet")) OR "Vaccine Induced Thrombocytopenia Syndrome" OR "vaccine-induced prothrombotic immune thrombocytopenia" OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia" OR " inflammatory and thrombotic response to vaccination" OR "Rare thromboembolic syndrome" OR VIPIT OR "Heparin induced thrombocytopenia"	353
# 2 – Thrombosis after COVID-19 vaccination	("Cerebral venous sinus thrombosis" OR " Cerebral venous thrombosis" OR "Sinus Thrombosis, Intracranial" OR "cerebral sinovenous thrombosis" OR "cerebral vein thrombosis" OR "cerebral venous and sinus thrombosis" OR "cerebral vein and dural sinus thrombosis" OR " cavernous sinus thrombosis" OR "deep venous thrombosis" OR "deep vein thrombosis" OR "diffuse intravascular thrombosis" OR "arterial thrombosis" OR CVST OR DVT OR "Disseminated Intravascular coagulation" OR "consumptive coagulopathy" OR "disseminated intravascular coagulopathy" OR "defibrination syndrome" OR "defibrinogenation syndrome" OR "acquired afibrinogenemia" OR "splanchnic vein" OR SVT OR "intra-abdominal thrombosis" OR "intra-abdominal venous thrombosis" OR "intra-abdominal vein thrombosis" OR "abdominal thrombosis" OR "venous thromboembolism" OR "pulmonary embolism" OR "pulmonary thromboembolism" OR Stroke OR "cerebrovascular accident" OR "CVA" OR "cerebral infarct" OR "ischemic infarctions" OR "CNS infarction" OR "myocardial infarction" OR "coronary infarction") AND (Innoculation* OR Immuniz* OR Vaccin* OR BNT162b2 OR "comirnaty" OR "mRNA-1273" OR CoviShield OR AZD1222 OR "Sputnik V" OR CoronaVac OR "BBIBP-CorV" OR "Ad26.CoV2.S" OR "JNJ-78436735" OR Ad26COVS1 OR VAC31518 OR EpiVacCorona OR Convidicea OR Ad5-nCoV OR Covaxin OR CoviVac OR ZF2001	256

	OR "NVX-CoV2373" OR "ZyCoV-D" OR CIGB 66 OR "CVnCoV" OR "INO-4800" OR "VIR-7831" OR "UB-612" OR BNT162 OR "Soberana 1" OR "Soberana 2" OR Pzifer OR Moderna OR "Pzifer/bioNtech" OR AstraZeneca OR Gamaleya OR Sinovac OR Sinopharm OR "johnson & Johnson" OR Janssen OR "CanSino Biologics" OR "Bharat Biotech" OR "wuhan institute" OR Chumakov OR "Longcom Biopharmaceutical" OR "Finlay Institute of Vaccines" OR Novavax OR "Zydus Cadila" OR "Center for Genetic Engineering and Biotechnology" OR CureVac OR "University of Melbourne" OR "Murdoch Children's Research Institute" OR "Radboud University Medical Center" OR "Faustman Lab" OR "Inovio Pharmaceuticals" OR Dynavax OR ImmunityBio OR NantKwest OR COVAXX OR "adenovirus vector")	

Pubmed

https://pubmed.ncbi.nlm.nih.gov/

Concept	Search string	Results
#3 - SR on TTS-like syndromes	"Heparin induced thrombocytopenia"[tiab] OR "Vaccine Induced Thrombocytopenia Syndrome"[tiab] OR "vaccine-induced prothrombotic immune thrombocytopenia"[tiab] OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia"[tiab] OR " inflammatory and thrombotic response to vaccination"[tiab] OR "Rare thromboembolic syndrome"[tiab] OR VIPIT[tiab] OR ((prothrombotic[tiab] OR thrombosis[tiab] OR thrombotic[tiab] OR thromboembolism[tiab] OR embolism[tiab] OR thrombus[tiab] OR D-dimer[tiab] OR "Splanchnic vein"[tiab] OR SVT[tiab] OR CVST[tiab] OR DVT[tiab] OR "Disseminated Intravascular coagulation"[tiab] OR "consumptive coagulopathy"[tiab] OR "disseminated intravascular coagulopathy"[tiab] OR "defibrination syndrome"[tiab] OR "defibrinogenation syndrome"[tiab] OR "acquired afibrinogenemia"[tiab] OR Stroke[tiab] OR "cerebrovascular accident"[tiab] OR "CVA"[tiab] OR "cerebral infarct"[tiab] OR "ischemic infarctions"[tiab] OR "CNS infarction"[tiab] OR "Myocardial Infarction"[tiab] OR "coronary infarction"[tiab]) AND ("thrombocytopenia"[tiab] OR thrombocytopenic[tiab] OR "Anti PF4 antibodies"[tiab] OR "platelet factor 4"[tiab] OR "low platelet"[tiab])) AND systematic[sb]	181

Global Index Medicus **https://pubmed.ncbi.nlm.nih.gov/**

Concept	Search string	Results
#4 - SR on TTS-like syndromes	"Heparin induced thrombocytopenia" OR "Vaccine Induced Thrombocytopenia Syndrome" OR "vaccine-induced prothrombotic immune thrombocytopenia" OR "Vaccine-Induced Immune Thrombotic Thrombocytopenia" OR " inflammatory and thrombotic response to vaccination" OR "Rare thromboembolic syndrome" OR VIPIT OR ((prothrombotic OR thrombosis OR thrombotic OR thromboembolism OR embolism OR thrombus OR D-dimer OR "Splanchnic vein" OR SVT OR CVST OR DVT OR "Disseminated Intravascular coagulation" OR "consumptive coagulopathy" OR "disseminated intravascular coagulopathy" OR "defibrination syndrome" OR "defibrinogenation syndrome" OR "acquired afibrinogenemia" OR Stroke OR "cerebrovascular accident" OR "CVA" OR "cerebral infarct" OR "ischemic infarctions" OR "CNS infarction" OR "Myocardial Infarction" OR "coronary infarction") AND ("thrombocytopenia" OR thrombocytopenic OR "Anti PF4 antibodies" OR "platelet factor 4" OR "low platelet")) AND (type_of_study:("guideline" OR "policy_brief" OR "systematic_reviews"))	14

WHO COVID-19 Database **https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/**

Concept	Search string	Results 18/10/2021
#1- COVID Vaccintion	"Coalition for Epidemic Preparedness Innovations" OR ti:CEPI OR COVAX or "ACT-Accelerator" OR Immunization* OR immunisation* OR vaccinat* OR innoculat* OR adenovirus-vector* OR virus-vector* OR Comirnaty OR BNT162b2 OR bnt-162 OR Pfizer-BioNTech OR Biontech-pfizer OR tozinameran OR Vaxzervria OR Oxford-astrazeneca OR astrazeneca-oxford OR astrazeneca OR azd-1222 OR azd1222 OR chadox-1-ncov-19 OR covishield OR serum-institute OR "johnson & Johnson" OR janssen-cilag OR janssen OR ad26.cov2.s OR ad26cov2s OR jnj-78436735 OR jnj78436735 OR Moderna-biotech OR mRNA-1273 OR elasomeran OR cx-024414 OR RNA-1273 OR coronavac OR picovacc OR Sinovac OR Sinopharm OR Bibp OR bbibp-Corv OR covaxin OR bbv-152 OR bbv-152a OR bbv-152b OR bbv-152c OR bharat-biotech OR Sputnik-V OR sputnik-light OR VAC31518 or EpiVacCorona or Convidicea OR "CanSino Biologics" OR Cansino-bio OR "Ad5-nCoV" or PakVac OR Novavax OR NVX-CoV2373 OR tak-019 OR covovax OR "COVIran Barakat" OR BBV152 OR WIBP-CorV OR KoviVac or CoviVac or ZF-2001 OR ZIFIVAX OR ZF-UZ-VAC-2001 OR "RBD-Dimer" or QazVac or "QazCovid-in" or "TAK-919" OR "ZyCoV-D" or "CIGB 66" or VLA2001 or CVnCoV OR Zorecimeran	17,491

	OR CV-07050101 OR curevac OR "INO-4800" OR reluscovtogene-ralaplasmid OR pGX9501 OR "VIR-7831" or "UB-612" or BNT162 or "GRAd-COV2" or "SCB-2019" or "Razi Cov Pars" or Nanocovax or "AdCLD-CoV19" or "KD-414" or "VBI-2902a" or "COVID-eVax" or "S-268019" or "GLS-5310" or Covigenix or "VAX-001" or "Vietnam domestic vaccine" or "EXG-5003" or "AKS-452" or "DS-5670a" or "ABNCoV2" or "Soberana 1" OR Soberana-01 OR Soberana-02 OR soberana-plus OR "Soberana 2" OR EuCorVac OR "IIBR-100" OR ArCov OR "AG0301-COVID-19" OR "GX-19N" OR "ARCT-021" "LUNAR-COV19" OR "HDT-301" OR HGCO19 OR "AV-COVID-19" OR "PTX-COVID-19-B" OR "COVI-VAC" OR CORVax12 OR "MVA-SARS-2-S" OR COH04S1 OR "AdimrSC-2f" OR "bacTRL-Spike" OR "COVAX-19" OR "DelNS1-2019-nCoV-RBD-OPT1" OR "GRAd-COV2" OR "UQ-CSL V451" OR "SCB-2019" OR "VXA-CoV2-1" OR "AdCOVID" OR "AAVCOVID" OR "ChAd-SARS-CoV-2-S" OR HaloVax OR LineaDNA OR MRT5500 OR PittCoVacc OR "T-COVIDTM" OR "LNP-nCoVsaRNA" OR V590 OR V591 OR "ERUCOV-VAC" OR ABNCoV2 OR BUTANVAC OR "Coviran barekat" OR MVC-COV1901 OR Epi-Vac-Corona OR COV2-PreS-dTM-AS03 OR Vidprevtyn OR Corbevax OR GBP510 OR BBV154 OR "Gam-COVID-Vac" OR GAM-KOVID-VAC OR ganulameran OR bnt-162b3 OR abdavomeran OR bnt-162b1 OR zorecimeran OR pidacmeran OR BNT-162c2 OR SCB-2019 OR AG-0302	
#2 Thrombosis – (CVST, DVT, DIC, AT, splanchnic, PE, Stroke, MI, Arterial thrombosis, Splenic, Hepatic)	prothrombotic OR thrombo* OR thrombotic OR thromboembolism OR embolism OR thrombus OR D-dimer OR headache OR abdominal-pain OR fever OR malaise OR light-headedness OR "Cerebral venous sinus thrombosis" OR " Cerebral venous thrombosis" OR "Sinus Thrombosis, Intracranial" OR "cerebral sinovenous thrombosis" OR "cerebral vein thrombosis" OR "cerebral venous and sinus thrombosis" OR "cerebral vein and dural sinus thrombosis" OR "cavernous sinus thrombosis" OR "deep venous thrombosis" OR "deep vein thrombosis" OR "diffuse intravascular thrombosis" OR "arterial thrombosis" OR "arterial embolism" OR CVST OR DVT OR "Disseminated Intravascular coagulation" OR "consumptive coagulopathy" OR "disseminated intravascular coagulopathy" OR "defibrination syndrome" OR "defibrinogenation syndrome" OR "acquired afibrinogenemia" OR "splanchnic vein" OR SVT OR "intra-abdominal thrombosis" OR "intra-abdominal venous thrombosis" OR "intra-abdominal vein thrombosis" OR "abdominal thrombosis" OR "venous thromboembolism" OR "pulmonary embolism" OR "pulmonary thromboembolism" OR Stroke OR "cerebrovascular accident" OR "CVA" OR "cerebral infarct" OR "ischemic infarctions" OR "CNS infarction" OR "myocardial infarction" OR "coronary infarction" OR splenic-infarct* OR splenic-thrombosis OR hepatic-thrombosis OR OR "Anti PF4 antibodies" OR "platelet factor 4"))	22,874
#3 -TTS Syndrome	"Vaccine Induced Thrombocytopenia" OR "vaccine induced prothrombotic immune thrombocytopenia" OR VIPIT OR "Vaccine Induced Immune Thrombotic Thrombocytopenia" OR VITT OR "Rare thromboembolic syndrome" OR "vaccine associated thrombocytopenia" OR "vaccine induced immune thrombocytopenia" OR "vaccine induced	176

	thrombosis" OR "vaccine related thrombocytopenia" OR "vaccine related thrombosis" OR " vaccine induced thrombotic thrombocytopenia syndrome" OR VITTS OR "Thrombosis with Thrombocytopenia Syndrome" OR "thrombotic thrombocytopenia syndrome" OR TTS OR "vaccine associated cerebral venous sinus thrombosis" OR "thrombotic thrombocytopenic purpura" OR TTP OR VATTS OR VATT	
#4 Combined – (#1 AND #2) OR #3	(("Coalition for Epidemic Preparedness Innovations" OR ti:CEPI OR COVAX or "ACT-Accelerator" OR Immunization* OR immunisation* OR vaccinat* OR innoculat* OR adenovirus-vector* OR virus-vector* OR Comirnaty OR BNT162b2 OR bnt-162 OR Pfizer-BioNTech OR Biontech-pfizer OR tozinameran OR Vaxzervria OR Oxford-astrazeneca OR astrazeneca-oxford OR astrazeneca OR azd-1222 OR azd1222 OR chadox-1-ncov-19 OR covishield OR serum-institute OR "johnson & Johnson" OR janssen-cilag OR janssen OR ad26.cov2.s OR ad26cov2s OR jnj-78436735 OR jnj78436735 OR Moderna-biotech OR mRNA-1273 OR elasomeran OR cx-024414 OR RNA-1273 OR coronavac OR picovacc OR Sinovac OR Sinopharm OR Bibp OR bbibp-Corv OR covaxin OR bbv-152 OR bbv-152a OR bbv-152b OR bbv-152c OR bharat-biotech OR Sputnik-V OR sputnik-light OR VAC31518 or EpiVacCorona or Convidicea OR "CanSino Biologics" OR Cansino-bio OR "Ad5-nCoV" or PakVac OR Novavax OR NVX-CoV2373 OR tak-019 OR covovax OR "COVIran Barakat" OR BBV152 OR WIBP-CorV OR KoviVac or CoviVac or ZF-2001 OR ZIFIVAX OR ZF-UZ-VAC-2001 OR "RBD-Dimer" or QazVac or "QazCovid-in" or "TAK-919" OR "ZyCoV-D" or "CIGB 66" or VLA2001 or CVnCoV OR Zorecimeran OR CV-07050101 OR curevac OR "INO-4800" OR reluscovtogene-ralaplasmid OR pGX9501 OR "VIR-7831" or "UB-612" or BNT162 or "GRAd-COV2" or "SCB-2019" or "Razi Cov Pars" or Nanocovax or "AdCLD-CoV19" or "KD-414" or "VBI-2902a" or "COVID-eVax" or "S-268019" or "GLS-5310" or Covigenix or "VAX-001" or "Vietnam domestic vaccine" or "EXG-5003" or "AKS-452" or "DS-5670a" or "ABNCoV2" or "Soberana 1" OR Soberana-01 OR Soberana-02 OR soberana-plus OR "Soberana 2" OR EuCorVac OR "IIBR-100" OR ArCov OR "AG0301-COVID-19" OR "GX-19N" OR "ARCT-021" "LUNAR-COV19" OR "HDT-301" OR HGCO19 OR "AV-COVID-19" OR "PTX-COVID-19-B" OR "COVI-VAC" OR CORVax12 OR "MVA-SARS-2-S" OR COH04S1 OR "AdimrSC-2f" OR "bacTRL-Spike" OR "COVAX-19" OR "DelNS1-2019-nCoV-RBD-OPT1" OR "GRAd-COV2" OR "UQ-CSL V451" OR "SCB-2019" OR "VXA-CoV2-1" OR "AdCOVID" OR "AAVCOVID" OR "ChAd-SARS-CoV-2-S" OR HaloVax OR LineaDNA OR MRT5500 OR PittCoVacc OR "T-COVIDTM" OR "LNP-nCoVsaRNA" OR V590 OR V591 OR "ERUCOV-VAC" OR ABNCoV2 OR BUTANVAC OR "Coviran barekat" OR MVC-COV1901 OR Epi-Vac-Corona OR COV2-PreS-dTM-AS03 OR Vidprevtyn OR Corbevax OR GBP510 OR BBV154 OR "Gam-COVID-Vac" OR GAM-KOVID-VAC OR ganulameran OR bnt-162b3 OR abdavomeran OR bnt-162b1 OR zorecimeran OR pidacmeran OR BNT-162c2 OR SCB-2019 OR AG-0302) AND (prothrombotic OR thrombosis OR thrombotic OR thromboembolism OR embolism OR	1,733

	thrombus OR D-dimer OR headache OR abdominal-pain OR fever OR malaise OR light-headedness OR "Cerebral venous sinus thrombosis" OR " Cerebral venous thrombosis" OR "Sinus Thrombosis, Intracranial" OR "cerebral sinovenous thrombosis" OR "cerebral vein thrombosis" OR "cerebral venous and sinus thrombosis" OR "cerebral vein and dural sinus thrombosis" OR "cavernous sinus thrombosis" OR "deep venous thrombosis" OR "deep vein thrombosis" OR "diffuse intravascular thrombosis" OR "arterial thrombosis" OR "arterial embolism" OR CVST OR DVT OR "Disseminated Intravascular coagulation" OR "consumptive coagulopathy" OR "disseminated intravascular coagulopathy" OR "defibrination syndrome" OR "defibrinogenation syndrome" OR "acquired afibrinogenemia" OR "splanchnic vein" OR SVT OR "intra-abdominal thrombosis" OR "intra-abdominal venous thrombosis" OR "intra-abdominal vein thrombosis" OR "abdominal thrombosis" OR "venous thromboembolism" OR "pulmonary embolism" OR "pulmonary thromboembolism" OR Stroke OR "cerebrovascular accident" OR "CVA" OR "cerebral infarct" OR "ischemic infarctions" OR "CNS infarction" OR "myocardial infarction" OR "coronary infarction" OR splenic-infarct* OR splenic-thrombosis OR hepatic-thrombosis OR "Anti PF4 antibodies" OR "platelet factor 4")) OR ("Vaccine Induced Thrombocytopenia" OR "vaccine induced prothrombotic immune thrombocytopenia" OR VIPIT OR "Vaccine Induced Immune Thrombotic Thrombocytopenia" OR VITT OR "Rare thromboembolic syndrome" OR "vaccine associated thrombocytopenia" OR "vaccine induced immune thrombocytopenia" OR "vaccine induced thrombosis" OR "vaccine related thrombocytopenia" OR "vaccine related thrombosis" OR " vaccine induced thrombotic thrombocytopenia syndrome" OR VITTS OR "Thrombosis with Thrombocytopenia Syndrome" OR "thrombotic thrombocytopenia syndrome" OR TTS OR "vaccine associated cerebral venous sinus thrombosis" OR "thrombotic thrombocytopenic purpura" OR TTP OR VATTS)	
#5 – Date filter Update	22/05/2021 – 20/10/2021	913

World Health Organization (WHO)
pvsupport@who.int

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