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

Interim guidance

19 July 2021

World Health Organization

WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

WHO reference number: WHO/2019-nCoV/TTS/2021.1

Contents

Abbreviations and acronyms

AEFI	Adverse event following immunization
aHIT	Autoimmune heparin-induced thrombocytopenia
Ad26.COV2-S vaccine	Johnson & Johnson (J&J) Janssen COVID-19 Ad26.COV2-S vaccine
APTT	Activated partial thromboplastin time
BC	Brighton Collaboration
ChAdOx-1 vaccine	AstraZeneca COVID-19 ChAdOx-1 vaccine
CT scan	Computerized tomography scan
CTPA	CT pulmonary angiogram
CVST	Cerebral venous sinus thrombosis
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
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)
HIT	Heparin induced thrombocytopenia
ITP	Idiopathic thrombocytopenic purpura
IVB	Immunizations, Vaccines and Biologicals Department
IVIG	Intravenous immunoglobulin
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
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PF4	Platelet factor 4
PICO	Patient/intervention/comparator/outcome)
QNS	Quality Norms and Standards
RPQ	Regulation and Prequalification
SMR	Standardized morbidity ratio
SVT	Splanchnic vein thrombosis
TTP	Thrombotic thrombocytopenic purpura
TTS	Thrombosis thrombocytopenia syndrome
WHE	WHO Health Emergencies Programme

Key points

Background	Thrombosis with thrombocytopenia syndrome (TTS) has been reported in individuals vaccinated with COVID-19 non-replicant adenovirus vector-based vaccines (AstraZeneca COVID-19 ChAdOx-1 vaccine and Johnson & Johnson (J&J) Janssen COVID-19 Ad26.COV2-S vaccine).
Scope	The present document aims to provide interim guidance on the recognition and management of thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccination.
Case definition	TTS is defined by the presence of a thrombosis/thromboembolism, generally in uncommon locations, such as cerebral venous sinus or splanchnic veins and marked thrombocytopenia (<50 x 10^9/L) following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine. Cases of thrombosis/thromboembolisms (i.e., pulmonary, deep vein thrombosis, coronary arteries, cerebral arteries) in common location have also been reported following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine.
Incidence	The cumulative incidence of TTS following vaccination with a non-replicant 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 and in patients aged <60 years. Most TTS cases have been reported within 3 to 30 days following vaccination with a COVID-19 non-replicant adenovirus vector-based vaccine. 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.
Risk factors	The main risk factors for TTS following vaccination with COVID-19 adenovirus vector-based vaccines are the use of non-replicant adenovirus vector-based vaccines and younger age. There is currently no evidence that traditional risk factors for thrombosis/thromboembolisms increase the risk of TTS in this context.
Pathophysiology	TTS has been associated with the presence of anti-platelet factor 4 (anti-PF4) antibodies. There are similarities with autoimmune heparin-induced thrombocytopenia (aHIT). TTS may be caused by the binding of anti-PF4 to platelets, causing platelet activation and aggregation, thrombosis, platelet consumption, and thrombocytopenia. However, the exact mechanisms are still unclear and should be further investigated.
Clinical presentation	TTS should be suspected in patients presenting with severe and unusual headache, abdominal pain with or without vomiting, sudden onset of breathing difficulty, chest pain or limb pains, particularly in those aged under 60 years, within four weeks following vaccination. Patients with suggestive clinical symptoms should promptly undergo investigations to rule out thrombotic events and presence of thrombocytopenia.
Laboratory diagnosis	Individuals who present with thrombosis within four weeks following vaccination 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 are not as sensitive. The presence of anti-PF4 antibodies in a patient with a thrombotic event and thrombocytopenia following COVID-19 vaccination is highly suggestive of TTS. Other biomarkers can be helpful in the laboratory diagnosis of TTS, including D-dimer, fibrinogen, and blood smear to confirm reduced platelets and to rule out platelet clumping. The case definition implies the absence of a better alternative explanation for the condition.

Imaging	Suitable 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.
Clinical case management	Vaccinated individuals should be advised to seek immediate medical attention if they develop symptoms including severe or persistent headache, blurred vision, shortness of breath, chest pain, leg swelling, persistent abdominal pain or unusual skin bruising and/or petechiae (tiny purple, red, or brown spots on the skin) occurring within four weeks after vaccination, although some cases have been reported later than 30 days post-vaccination. These patients should be investigated for thrombosis and thrombocytopenia. Reporting these symptoms must be made easy for the vaccine recipients, and could include helplines and hospital vaccine centre, online reporting systems.
Treatment	WHO advises against the use of heparin in individuals with TTS in the context of COVID-19 vaccination (*conditional recommendation, very low certainty*). WHO recommends against the use of platelet infusion for individuals with TTS in the context of COVID-19 vaccination in all cases other than emergency situations where surgery is strongly indicated, thrombocytopenia is severe (platelets <50 000/μL), and platelet transfusion is required to be able to proceed with emergency surgery *(strong, very low certainty).* WHO recommends the use of intravenous immunoglobulins (IVIG) and/or non-heparin-based anticoagulants for individuals with TTS following COVID-19 vaccination *(strong, very low certainty).* WHO does not provide any recommendation for steroid treatment, but notes the general use of steroids and the likelihood that steroids will usually be given in combination with other treatments.

Background, scope, and rationale

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) Janssen 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 adenovirus vectored vaccines and the events (1-3).

The association was based on the temporal association with vaccination, an increased incidence when compared with expected baseline rates, for cerebral venous sinus thrombosis (CVST), the presence of simultaneous multiple thromboses in some patients, the presence of thrombocytopenia and anti-platelet factor 4 antibodies (anti-PF4), and a higher mortality rate than that reported in the literature (1-30).

The purpose of this document is to provide interim guidance on the recognition and clinical management of this rare adverse event, known as thrombosis with thrombocytopenia syndrome (TTS), following vaccination. This newly reported syndrome has received different names, including vaccine-induced immune thrombotic thrombocytopenia (VIITT), vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), and vaccine-induced thrombotic thrombocytopenia (VITT). **In the present document, the term TTS will used in the context of COVID-19 adenovirus-vector vaccines unless otherwise specified.**

Knowledge about TTS 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 healthcare providers in the assessment and management of potential TTS cases. Individuals and healthcare 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 given and which should be avoided. This document reviews the existing information on the epidemiology, risk factors, aetiology, diagnosis and clinical management protocol for TTS with specific considerations for low-and-middle income countries (LMICs). It will be revised as new evidence emerges. Detailed data regarding the methodology used in the guideline development is available in Annex 5: Methods for guideline development. TTS is a very rare adverse event following immunization (AEFI) and the benefits of COVID-19 vaccination clearly outweigh the potential risks.

Case definition

An interim case definition that could be practical to use in clinical settings has been developed with input from a representative of the Brighton Collaboration (BC) group, to ensure the harmonization with the BC definition of TTS (*version 10.16.3-May-23-2021*). The present interim case definition aims to provide an optimal balance between sensitivity and specificity while ensuring applicability across all resource settings. It is based on the existing evidence and as needed, can be updated with the publication of new cases and data (32).

It is important to note that there is a difference between the clinical management of a potential case, and the case definition. The clinical management algorithms (see below) aim to identify all possible cases with the intent of offering the most adequate treatments while continuing to confirm or rule out TTS, and avoid potentially harmful treatments. Since platelet counts can evolve over time and results for some investigations are not available instantly, the classification of cases should ideally be finalized once all available and existing data have been analysed. The investigations must be repeated if symptoms do not resolve.

The definition of TTS is based on the combined presence of a thrombosis and new onset thrombocytopenia (**Table 1**). Three levels of certainty are proposed, based on the anatomical location of the thrombosis, the severity of thrombocytopenia and the outcome of laboratory investigations (**Table 2**). The most common thromboses in the general population are limb vein thrombosis, pulmonary artery/vein thrombosis, cerebral artery thrombosis or myocardial artery thrombosis. However in the case of TTS, the thromboses have been observed mainly in cerebral and splanchnic veins. Multiple-organ thromboses have also been observed, although less commonly. In view of these observations, the term ‘unusual location’ thrombosis is used to describe the thromboses in TTS.

WHO classification of TTS following vaccination with a COVID-19 vaccine is based on the degree of certainty (**Table 2**). It includes three mandatory criteria (A, B and C) with C defining the degree of certainty based on the combination of major and minor criteria presented in **Table 1**:

A. Vaccination against COVID within last 30 days.
B. No alternative explanation for the condition (i.e., no heparin exposure within the previous 100 days).
C. Combination of thrombosis and thrombocytopenia.

Table 1: Major and minor criteria for thrombocytopenia, thrombotic events and laboratory examinations.

Classification	Major criteria	Minor criteria
Thrombosis	**CONFIRMED** diagnosis of thrombosis by imaging study, surgical, or pathology findings consistent with thrombosis/thromboembolism in an **uncommon location**: • cerebral veins OR • splanchnic veins OR • multiple organ	**CONFIRMED** diagnosis of thrombosis by imaging study, surgical, or pathology consistent with thrombosis/thromboembolism in a **common location:** • pulmonary arteries/veins OR • limb veins OR • coronary arteries OR • cerebral arteries OR • other arteries/veins OR **SUGGESTIVE** thrombosis by supporting imaging or laboratory findings **suggestive but not definitive** of thrombosis/thromboembolism in any location OR **SUGGESTIVE** thrombosis by specific **clinical syndromes** consistent with thrombosis or thromboembolism event in any location
Thrombocytopenia	Platelet count: <50 x 10^9/L AND Confirmatory peripheral smear showing reduced platelets AND No evidence of platelet clumping	Platelet count: > 50 x 10^9/L - <150 x 10^9/L OR >50% decrease from baseline platelet count
Laboratory (other than thrombocytopenia)	Positive anti-platelet factor 4 antibodies (with ELISA) or platelet functional assay (i.e., serotonin release assay)	D-dimer > 4000 µg/L fibrinogen equivalent units (FEU)

Table 2. WHO classification of TTS following vaccination with a COVID-19 vaccine is based on the degree of certainty.

Classification	Level 1 (Confirmed case)		Level 2 (Probable case)		Level 3 (Possible case)
Thrombosis	Major /	Major	Minor	Major	Minor