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TECHNICAL BRIEF

Adverse Events of Special Interest (AESIs) for COVID-19 Vaccines Surveillance

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Introduction

Following the authorization of novel Coronavirus Disease 2019 (COVID-19) vaccines in Canada, post-marketing surveillance is being conducted to monitor the safety of these new vaccines throughout the implementation of the immunization program. Provincial reporting of adverse events following immunization (AEFIs) to Canada's AEFI Surveillance System (CAEFISS) is an important component of post-marketing surveillance in Canada.

An AEFI is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of a vaccine.[1] Reporting of adverse events of special interest (AESIs) for COVID-19 vaccines in the context of overall AEFI surveillance enables enhanced monitoring by pre-specifying events which may otherwise not be captured or readily analyzed from a passive surveillance system. In addition to AESIs identified before the launch of COVID-19 vaccine programs, this document outlines guidance for the reporting of events identified through post-marketing surveillance and continues to be the focus of enhanced monitoring (e.g., thrombosis with thrombocytopenia syndrome (TTS) following viral vector vaccines and myocarditis/pericarditis following mRNA vaccines).

Purpose

This document outlines preliminary information and Brighton Collaboration case definitions (where available) related to Public Health Unit reporting of AESIs associated with **administration of COVID-19 vaccine**. This document should be used in conjunction with Appendix B: Provincial Case Definitions for Diseases of Public Health Significance for AEFIs,[2] which sets out the overarching provincial case definitions for AEFI reporting for all vaccines.

This document includes a list of AESIs for COVID-19 vaccines that have been identified to date by the Public Health Agency of Canada (PHAC) and international health authorities, including the Brighton Collaboration and World Health Organization (WHO). The AESIs that are described within this document were originally selected based on a theoretical rationale for a possible association with COVID-19 vaccines. For example, they include events that may occur during the clinical course of SARS-CoV-2 infection or as a complication of infection. For this reason, collecting and documenting recent history of COVID-19 infection is an important component of the reporting process for all AESIs.

Given the rapidly evolving state of information related to COVID-19 disease and vaccines, this document will be updated as new information becomes available, including updating current and any forthcoming standardized case definitions from the Brighton Collaboration. A list of current and forthcoming Brighton Collaboration case definitions for AESIs can be found in the Appendix. **If you have any questions regarding reporting of COVID-19 AEFIs or AESIs, please contact the immunization team at Public Health Ontario (PHO) at ivpd@oahpp.ca.**

Types of Adverse Events

*In the absence of established temporal criteria for the reporting of COVID-19 AESIs, PHUs may consider using **42 days** as the upper limit for time to onset following vaccination. This aligns with temporal criteria used for some AEFIs following other inactivated vaccines.[2] Temporal criteria are intended to support implementation of passive vaccine safety surveillance and are provided only as guidance for PHUs to assist with AEFI reporting. AEFIs which occur outside of these timelines may still be reported if the event is assessed as clinically significant.*

Vaccine-associated Enhanced Disease

A physician-diagnosed illness occurring in an individual who receives a vaccine and is subsequently infected with the pathogen that the vaccine is meant to protect against.[3]

Vaccine-associated enhanced disease (VAED) is reportable if the vaccine recipient:[4]

- Develops laboratory confirmed SARS-CoV-2 infection after receiving the first or second dose of COVID-19 vaccine

AND

- Has severe and/or modified/unusual clinical symptoms compatible with COVID-19 infection (as determined by the attending physician)

AND/OR

- Is hospitalized

Discussion:

VAED may present as severe disease or modified/unusual clinical manifestation(s) of disease in an individual exposed to a wild-type pathogen after previously receiving a vaccination for the same pathogen.[3] This adverse event category is **not** intended to be used to capture all cases of lab-confirmed infection following immunization. A diagnosis of lab-confirmed SARS-CoV-2 infection without additional clinical criteria of severity does not meet the case definition; a physician-diagnosis of VAED is required.

VAED is a known adverse event associated with some vaccines that are not currently in use; for example formalin-inactivated respiratory syncytial virus (RSV) vaccine, which was investigational only (e.g., never brought to market) and formalin-inactivated measles vaccine, which has not been used for decades.[3] Randomized clinical trials have looked for VAED as a specific outcome and there is no evidence of an association between VAED and authorized COVID-19 vaccines. Further information on VAED is available from the Brighton Collaboration.[3]

Multisystem Inflammatory Syndrome in Children and Adults

A physician-diagnosed acute illness in children/young adults under 21 years of age (MIS-C) or adults 21 years of age and older (MIS-A) that is characterized by a hyperinflammatory response including persistent fever and multi-organ involvement (MIS-A may not be accompanied by fever).[5]

Discussion:

Multisystem inflammatory syndrome in children and adults (MIS-C, MIS-A) is a rare complication of SARS-CoV-2 infection. It is characterized by persistent fever in children, and a constellation of symptoms, including multi-organ (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic, neurologic, hepatic) involvement and elevated inflammatory markers.[5,6] In children presenting with signs and symptoms consistent with MIS-C, the differential diagnosis is broad and includes other infectious and inflammatory conditions including Kawasaki disease (KD).[7] In both children and adults with MIS-C or MIS-A respectively, the differential diagnosis includes Steven-Johnson's syndrome (SJS), toxic epidermal necrolysis (TEN), and toxic shock syndrome (TSS).[5,7] Further information on MIS-C/A is available from the Brighton Collaboration.[5]

Acute Respiratory Distress Syndrome

An acute illness characterized by progressive symptoms of dyspnea, tachypnea and hypoxemia that is physician-diagnosed as acute respiratory distress syndrome (ARDS).[8]

Discussion:

ARDS is a manifestation of acute lung injury, commonly resulting from sepsis, trauma, and severe pulmonary infection.[9] Clinically, it is characterized by diffuse alveolar damage with hypoxemia and poor lung compliance.[10] Further information on ARDS is available from the Brighton Collaboration.[10]

Acute Cardiovascular Injury

An acute illness that is physician-diagnosed as a cardiovascular injury.

Discussion:

Acute cardiovascular injury refers to a broad spectrum of cardiac pathology including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, myocarditis, pericarditis and cardiac arrhythmias, usually associated with abnormalities on ECG, echocardiography or cardiac MRI, and elevated biochemical markers.[4] **Note:** Reports of myocarditis and pericarditis should be captured under "Myocarditis/Pericarditis" (see below).

Myocarditis/Pericarditis

A condition that is physician diagnosed and is characterized as inflammation of the heart muscle (myocarditis) or inflammation of the lining around the heart (pericarditis). This also includes myopericarditis or perimyocarditis, which are diagnoses that may be used for patients who meet criteria for both myocarditis and pericarditis.

Discussion:

Myocarditis and pericarditis are inflammatory diseases of the cardiac muscle and lining, respectively, caused by a variety of infectious and non-infectious conditions.[11] Infection with SARS-CoV-2 has been associated with cardiovascular complications, including myocarditis and pericarditis.[12-14] Symptoms can include chest pain, shortness of breath, or the feeling of a rapid or abnormal heart rhythm.[11] Symptoms may be accompanied by abnormal tests (e.g., electrocardiogram, serum troponins, echocardiogram).[11]

Recently there have been very rare reports of myocarditis (and pericarditis) following mRNA vaccination both in Canada and internationally.[15] Reported cases to date have occurred most frequently: in adolescents and younger adults (under 30 years of age), males and after the second dose of vaccine.[11] The majority of cases have been mild with individuals recovering quickly.[11] For further information on the current situation, please see PHO's At a Glance document on this topic.[16] As a precautionary measure, the National Advisory Committee on Immunization (NACI) is recommending that individuals who have experienced myocarditis or pericarditis following vaccination with a first dose of COVID-19 mRNA vaccine should defer the second dose until further information is available.[11]

The Brighton Collaboration has developed case definitions for both myocarditis[17] and pericarditis[18]. The Brighton myocarditis and pericarditis case definitions include various levels of diagnostic certainty, with level 1 being the most specific for this condition.

Level 1 of certainty (definitive case) for myocarditis is defined by elevated myocardial biomarkers (troponins) AND abnormal imaging study (either abnormal cardiac magnetic resonance (cMR) OR abnormal echocardiogram).[17]

The Brighton case definition for pericarditis level 1 of certainty (definitive case) is defined by at least two out of three of: i) evidence of abnormal fluid collection or pericardial inflammation by imaging study (echocardiogram, cMR or computed tomography (CT)); ii) physical exam finding(s) of a pericardial friction rub and/or pulsus paradoxus on examination; and iii) abnormal EKG findings (new and/or normalizes on recovery).[18] Further information on myocarditis and pericarditis is available from the Brighton Collaboration.

It is important, when possible, to rule out other possible causes of myocarditis/pericarditis such as bacterial and viral infections including SARS-CoV-2, auto-immune or connective tissue disease, malignancy, or toxins.[17,18] It is also important to rule out other causes of symptoms (e.g., myocardial infarction, pulmonary embolism, mediastinitis).[17,18]

Note: There is no expectation for PHUs to use Brighton Collaboration case definitions to rule out AEFI reports if there is a physician diagnosis of myocarditis or pericarditis. These resources can be used to provide helpful guidance on information to collect as part of the AEFI investigation.

Coagulation Disorders (including thrombotic events)

A condition that is physician-diagnosed and is characterized by abnormalities in the body's ability to control blood clotting leading to either excessive bleeding or thrombosis.

Discussion:

Coagulation disorders affect the body's ability to control blood clotting and can include both hemorrhagic and thrombotic events. Examples of specific diagnoses include thrombotic and

thromboembolic events both venous (e.g., cerebral venous sinus thrombosis (CVST), pulmonary embolism (PE), deep venous thrombosis (DVT)) and arterial (e.g., ischemic stroke, myocardial infarction). Please see the draft Brighton Collaboration case definition of thrombosis and thromboembolism for more information.[19] This AESI grouping also includes haemorrhagic disease, bleeding disorders, other coagulation disorders (e.g., disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS), complement disorder). Severe COVID-19 has been associated with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections (e.g., DIC or thrombotic microangiopathy).[20]

Note: Thrombocytopenia on its own is reportable as per Appendix B ("E.1 Thombocytopenia"), while thrombosis with thrombocytopenia should be reported as an AESI ("Thrombosis with Thrombocytopenia (TTS) and Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)," see below).

Thrombosis with Thrombocytopenia Syndrome (TTS) and Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

Thrombosis with Thrombocytopenia Syndrome (TTS) is a condition that is physician-diagnosed and is characterized by the presence of acute venous or arterial thrombosis/thromboembolism AND new onset thrombocytopenia.[21] Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) refers to the clinical syndrome of TTS, in addition to laboratory tests that confirm platelet activation (i.e., anti-platelet 4 antibodies).[22]

Discussion:

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is an autoimmune thrombotic process that has been observed to occur approximately 4-28 days following vaccination with adenoviral vector vaccines. The first identification of this clinical syndrome occurred following AstraZeneca COVID-19 vaccine, although it has now also been identified in association with Janssen vaccine.[22,23]

VITT may present with venous clots (e.g., PE, DVT, portal vein thrombosis, CVST) or arterial clots (myocardial infarction, stroke), in association with new onset thrombocytopenia (i.e., platelet count < 150 x 10^9/L).[22] Symptoms of VITT may include severe or persistent headache, focal neurological symptoms, seizures, blurred or double vision, limb swelling, redness, pallor or coldness.[22]

The Brighton Collaboration has recently released a draft case finding definition for Thrombosis with Thrombocytopenia Syndrome (TTS).[21] Level 1 of diagnostic certainty requires confirmation of thrombosis/thromboembolism by imaging study, surgical (e.g., thrombectomy), or pathological findings and new onset of thrombocytopenia.[21] Within each level of diagnostic certainty, cases are stratified based on recent exposure to heparin (i.e., within 100 days of symptom onset). The Ontario Science Table has released a brief on VITT that provides a diagnostic algorithm for VITT, including laboratory tests required for confirmation.[22] These tests are ordered following the detection of thrombosis with thrombocytopenia and include tests to identify anti-platelet 4 antibodies.

Note: All cases of TTS, regardless of whether or not the laboratory tests required to confirm the diagnosis of VITT are available, should be reported to PHO on the same day the public health unit (PHU) receives notification.

Acute Kidney Injury

An acute impairment of kidney function that is physician-diagnosed, characterized by a decline in urine output and an elevation of creatinine levels.[24]

Discussion:

Acute kidney injury is a broad clinical syndrome encompassing various aetiologies including specific kidney diseases (e.g. acute interstitial nephritis) and non-specific conditions (e.g. renal ischemia).[25]

Acute Liver Injury

An acute illness that is physician-diagnosed and occurs without preceding chronic liver disease.[26]

Discussion:

Acute liver injury is an illness of variable severity that occurs in persons who develop clinical symptoms of hepatotoxicity and/or laboratory evidence of elevated liver enzymes and/or altered liver function.[4] Illness occurs rapidly usually in a person who has no pre-existing liver disease.

Anosmia and/or Ageusia

A condition characterized by subjective loss of sense of smell (anosmia) and/or taste (ageusia) that is not associated with trauma, respiratory infections (e.g., influenza) or previously diagnosed medical condition manifesting as anosmia or ageusia.[4]

Discussion:

Smell and taste disorders may be attributable to a number of causes including, inflammatory conditions of the nasal sinuses, infections (e.g., SARS-CoV-2), head trauma, medication side effects, neurological disorders and aging.[27,28]

Chilblain – like Lesions

A cutaneous manifestation resembling chilblains that is physician-diagnosed, characterized by erythematous, edematous or blistering skin lesions that mostly commonly affect the toes and extremities.[29]

Discussion

Chilblain-like lesions are a dermatological finding that has been described in relation to COVID-19 disease.[29] Chilblains (perniosis) are an inflammatory skin condition typically occurring as an abnormal vascular response to the cold[30] whereas chilblain-like lesions are attributed to inflammatory or embolic microvascular occlusion,[31] occurring in the toes, feet, fingers and/or hands.[32] The lesions have been described as erythematous, purplish patches and papules, sometimes evolving towards erosions, pigmentation and scaling.[33] Chilblain-like lesions have been reported to occur predominantly in younger, otherwise asymptomatic patients[31] and may represent a post-viral or delayed-onset process, as developing lesions occur after the onset of other symptoms.[34]

Single Organ Cutaneous Vasculitis

A physician-diagnosed syndrome characterized by clinical and histological features of small vessel vasculitis of the skin without systemic involvement.[4,35]

Discussion:

Cutaneous vasculitis (CV) encompasses a wide range of entities characterized by inflammation of cutaneous (skin) blood vessels, with the term "single-organ vasculitis" referring to vasculitis affecting arteries/veins of any size in a single organ, without features suggesting systemic vasculitis.[36] Typically cases manifest with a single crop of lesions consisting of palpable purpura (hemorrhagic papules), erythematous papules, urticarial lesions, vesicles and hemorrhagic vesicles.[35] Lesions are usually asymptomatic, or associated with burning, pain or pruritus.[35] Single organ cutaneous vasculitis may be challenging to distinguish from systemic vasculitis.[37] Further information on single organ cutaneous vasculitis is available from the Brighton Collaboration.[35]

Erythema Multiforme

An acute, physician-diagnosed, immune-mediated dermatologic condition, with or without mucosal involvement.[38]

Discussion:

Erythema multiforme is characterized by the appearance of distinctive target lesions, with concentric colour variations, sometimes accompanied by oral, genital, and/or ocular mucosal erosions.[38] The clinical manifestations of erythema multiforme can vary and target lesions may not be present in all patients.[38] The earliest lesions are typically round, erythematous, edematous papules surrounded by areas of blanching.[38] The papules can enlarge and develop concentric alterations in morphologic features and color, which results in the well-known target lesions. Lesions typically appear over three to five days and resolve over one to two weeks.[38]

Erythema multiforme is most commonly caused by herpes simplex virus (HSV) infection and certain medications. Laboratory testing can be used to support infectious associations. Although usually self-limiting, in a subset of individuals frequent episodes of erythema multiforme over many years can lead to recurrent disease. [38]

Acute pancreatitis

A condition that is physician-diagnosed, involving acute inflammation of the pancreas.[39,40]

Discussion:

Acute pancreatitis typically presents as acute onset of severe and constant abdominal pain radiating to the back, that is associated with vomiting and fever.[39] Disease presentation may range from mild (80%) with spontaneous resolution within several days, to severe (20%) requiring hospitalization. Acute pancreatitis is primarily caused by biliary disease (i.e., gallstones), alcohol consumption, and hypertriglyceridemia.[39,40] Clinical diagnosis is based on history and physical examination, along with laboratory (an elevated serum amylase or lipase greater than three times the upper limit of normal) and radiological investigations (e.g., ultrasound or computed tomography).[39,40]

Rhabdomyolysis

A condition that is physician-diagnosed, involving damage and injury of skeletal muscles.[41]

Discussion:

Clinical presentation of rhabdomyolysis may range from an asymptomatic illness with incidental elevation in the creatinine kinase (CK), to symptomatic weakness, limb swelling, and myalgia (e.g., shoulders, thighs, back, calves) secondary to tissue necrosis. [41] Laboratory investigation abnormalities include elevated CK levels, electrolyte imbalances, acute renal failure (ARF) and disseminated intravascular coagulation (DIC) due to the direct release of intracellular components such as CK, myoglobin, electrolytes and lactate dehydrogenase, into the bloodstream and extracellular space. [41] Due to high levels of red-pigmented myoglobin in the blood, urine may be reddish-brown or tea-coloured. The diagnosis is confirmed based on clinical symptoms and history, with laboratory investigations demonstrating elevated CK, and possibly elevated LDH, and myoglobin. [41] Rhabdomyolysis is most commonly caused by direct physical trauma (e.g., electric shock, crush injury) but can also be caused by infections (e.g., influenza, HIV, cytomegalovirus, varicella zoster virus, herpes simplex virus), muscle ischemia (e.g., compartment syndrome), overexertion, prolonged bed rest, and medications (e.g., statins). [41]

Subacute thyroiditis

A condition that is physician-diagnosed, involving inflammation of the thyroid.[42]

Discussion:

Subacute thyroiditis (SAT) characteristically presents clinically as either a painful or painless swelling of the thyroid gland associated with signs and symptoms of either hyperthyroidism (thyrotoxicosis) or hypothyroidism.[42]

Patients with the classic, painful (i.e., DeQuervain's) SAT, present with painful swelling of the thyroid which may initially be unilateral but usually spreads to involve the whole gland. [42] Common systemic symptoms include a low grade fever, malaise, fatigue, myalgia and arthralgia. Disease symptomatology includes a painful thyroid gland typically extending over 1 to 2 weeks with continuing fluctuating intensity for 3 to 6 weeks. Laboratory investigation demonstrates a very high erythrocyte sedimentation rate (ESR), and elevated C-reactive protein (CRP) and thyroglobulin with thyroid function test (e.g., thyroid stimulating hormone (TSH), free thyroxine) abnormalities. [42]

Painless subacute thyroiditis, also known as silent SAT occurs spontaneously due to an autoimmune process. [42] It occurs following 4-10% of pregnancies, referred to as postpartum thyroiditism but also presents as Grave's disease. The combination of thyroid enlargement without discomfort and positive anti-thyroid antibodies, associated with thyroid function test abnormalities, over a 9-12 month course is suggestive of painless SAT. [42]

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Appendix

Status of Brighton Collaboration case definitions for COVID-19 AESIs (as of July 2021)[43]

AESI	Brighton Collaboration case definition status
Vaccine-associated enhanced disease (VAED)	https://doi.org/10.1016/j.vaccine.2021.01.055
Multisystem inflammatory syndrome in children or adults (MIS-C/A)	https://doi.org/10.1016/j.vaccine.2021.01.054
Acute respiratory distress syndrome (ARDS)	10.1016/j.vaccine.2021.01.053
Acute cardiovascular injury	See below for myocarditis and pericarditis case definitions. Others not yet started
Coagulation disorders	• Thrombosis and thromboembolism (draft case definition) • Thrombosis with thrombocytopenia syndrome (TTS) (interim case definition) • Thrombocytopenia—as per Appendix B, based on existing Brighton Collaboration case definition
Acute kidney injury	Published lab-based criteria as suggested by the Brighton Collaboration*
Acute liver injury	Published lab-based criteria as suggested by the Brighton Collaboration**
Anosmia, ageusia	Working group to be formed
Chilblain – like lesions	Working group to be formed
Single Organ Cutaneous Vasculitis	10.1016/j.vaccine.2016.09.032
Erythema multiforme	Not yet started
Acute pancreatitis (NEW)	Not yet started
Rhabdomyolysis (NEW)	Not yet started
Subacute thyroiditis (NEW)	Not yet started
Thrombosis with thrombocytopenia syndrome (TTS)	Interim case definition available: https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition/
Myocarditis	Case definition available at: https://brightoncollaboration.us/myocarditis-case-definition-update/
Pericarditis	Case definition available at: https://brightoncollaboration.us/myocarditis-case-definition-update/

* Acute kidney injury – international consensus definition proposed by the Kidney Disease Improving Global Outcomes expert consensus group (www.kdigo.org):

- Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 umol/l) within 48 hours; OR
- Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR
- Urine volume ≤ 0.5 ml/kg/hour for 6 hours

**Acute liver injury – definition as used in majority of COVID-19 publications (but no international consensus):[43]

- > 3-fold elevation above the upper normal limit for ALT or AST OR
- > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP

Summary of Revisions

New material in this revision is highlighted in the table below.

Section	Revision	Implementation Date
Purpose	Addition of guidance for data collection on recent history of COVID-19 infection and information on enhanced surveillance activity for coagulation disorders including thrombotic events.	05/10/2021
Vaccine-associated enhanced disease	Additional information added to the case definition and discussion outlining which cases of VAED are reportable.	05/10/2021
Multisystem inflammatory syndrome in children	Addition of multisystem inflammatory syndrome in adults (MIS-A) in alignment with the Brighton Collaboration case definition for this adverse event.	05/10/2021
Acute respiratory distress syndrome	Case definition updated to provide clarity on what is considered reportable.	05/10/2021
Acute cardiovascular injury	Additional detailed related to clinical findings added to the discussion.	05/10/2021
Coagulation disorders	Addition of “thrombotic events” to the adverse event category and an expanded list of coagulation disorders and thrombotic events in the discussion.	05/10/2021
Thrombosis with Thrombocytopenia Syndrome (TTS) and Vaccine-induced immune thrombotic thrombocytopenia (VITT)	Addition of a new adverse event recently identified as an AESI for COVID-19 vaccine.	05/10/2021
Acute liver injury	Additional detail describing acute liver injury added to the discussion.	05/10/2021
Anosmia and/or ageusia	Case definition updated provide clarity on what is considered reportable.	05/10/2021
Single organ cutaneous vasculitis	Case definition and discussion updated to reflect the most current information available from the Brighton Collaboration.	05/10/2021

Section	Revision	Implementation Date
Acute pancreatitis	Addition of a new adverse event recently identified by the Brighton Collaboration as an AESI for COVID-19 vaccine.	05/10/2021
Rhabdomyolysis	Addition of a new adverse event recently identified by the Brighton Collaboration as an AESI for COVID-19 vaccine.	05/10/2021
Subacute thyroiditis	Addition of a new adverse event recently identified by the Brighton Collaboration as an AESI for COVID-19 vaccine.	05/10/2021
Appendix	Appendix added outlining status of Brighton Collaboration case definitions for COVID-19 AESIs	05/10/2021
Types of adverse events	Addition of information related to temporal criteria for reporting AESIs	07/22/2021
Myocarditis/pericarditis	Addition of a new adverse events recently identified as an AESI for COVID-19 vaccine.	07/22/2021
Thrombosis with Thrombocytopenia Syndrome (TTS) and Vaccine-induced immune thrombotic thrombocytopenia (VITT)	Case definition updated to exclude criteria for heparin exposure to align with the updated national case definition. Information in the discussion section updated to align with the updated national and interim Brighton Collaboration case definitions.	07/22/2021
Appendix	Appendix updated with links to publications for case definitions and draft/interim case definitions where available.	07/22/2021

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