Canadian Case Definition for Thrombosis with Thrombocytopenia Syndrome Following Vaccination

Any patient presenting with both new onset of: A) thrombocytopenia **AND** B) thrombosis or thromboembolism (as defined below), with:

- ☐ No known exposure to heparin within 100 days of symptom onset
- ☐ No other underlying condition or explanation for the condition
- ☐ Onset within 6 weeks (42 days) of vaccination

A. THROMBOCYTOPENIA

- ☐ Number of platelets less than 150 X 10^9/L (150,000/mm^3)

AND

B. THROMBOSIS OR THROMBOEMBOLISM

Definite Case

Confirmatory findings consistent with venous or arterial thrombosis/thromboembolism, including any of the following, depending on the location of the lesion:

- ☐ Imaging study (see full list in Appendix A)

OR

- ☐ Procedure (e.g., thrombectomy)

OR

- ☐ Pathology (e.g., biopsy or autopsy)

Probable Case

Clinical presentation consistent with thrombosis or thromboembolism event, including any of the following:

- ☐ Specific clinical syndromes (see full list in Appendix A)

AND

- ☐ Supporting Imaging or laboratory findings suggestive but not definitive of thrombosis/thromboembolism including any of the following
  - Chest radiograph
  - Echocardiogram
  - Computed tomography without contrast

OR

  - D-dimer - elevated above the upper limit of normal for age

Possible Case

Clinical presentation consistent with thrombosis or thromboembolism event, including any of the following:

- ☐ Specific clinical syndromes (see full list in Appendix A)

Additional Information

1. **Subtyping based on anti-PF4 status**

   A. Anti-PF4 positive/**VIPIT/VITT*** – either screening binding assay or functional assay positive
   B. Anti-PF4 pending – screening binding or functional assay pending (please note: screening binding assay may be falsely negative, as there is heterogeneity in the sensitivity of screening assays used across Canada)
   C. Anti-PF4 negative – negative functional assay
   D. Anti-PF4 unknown – unknown if tests were ordered

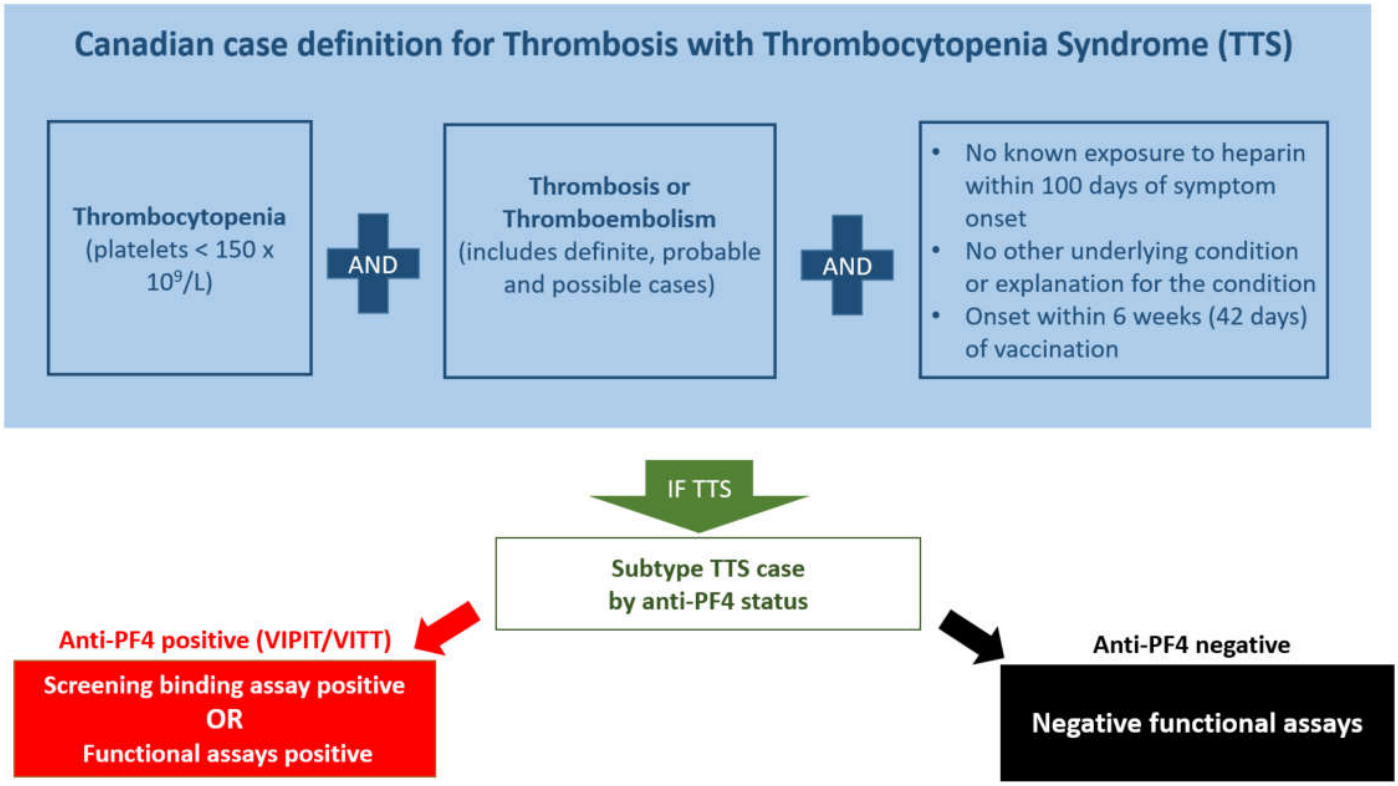
   *TTS cases with anti-PF4 positive results have a high likelihood of being an adenovirus vector COVID-19 vaccine-related reaction, according to current understanding. **In clinical medicine, these cases have been referred to as VITT (Vaccine-Induced Immune Thrombotic Thrombocytopenia) or VIPIT (Vaccine-Induced Prothrombotic Immune Thrombocytopenia)** after the publication of case series reports of patients in Europe that identify this biomarker as being associated with cases reviewed. Since then, multiple international surveillance systems have early data that consistently point towards an association between adenovirus vector COVID-19 vaccines and TTS, including in the US, UK, and Europe. As such, these events are increasingly understood to be causally associated with adenovirus vector vaccines. The strength of evidence pointing to a causal association is continually being reviewed as it evolves. **As with all other serious AEFIs and AESIs, each case of TTS following adenovirus vector vaccination requires medical case review by at least two physicians with expertise in causality assessment to classify consistency with a causal association, using the WHO causality assessment of an adverse event following immunization guidance. These reviewers may flag complex cases for further expert review, as may Federal/Provincial/Territorial/Indigenous public health jurisdictions**.

2. **COVID-19 laboratory testing to rule out current and past infection -** to aid in the determination of consistency with causal association to vaccination

3. **Other investigations to rule out other causes of thrombocytopenia and thrombosis,** to aid in diagnostic certainty and support causality assessments
   a. The current TTS definition does not require a peripheral smear to rule out clumping; however, it would increase diagnostic certainty, as would one more symptoms or signs of spontaneous bleeding if a peripheral smear is unavailable, as per the Brighton Collaboration case definition for thrombocytopenia.

4. **Please reference Brighton Collaboration case definitions for Thrombocytopenia, Thrombosis/thromboembolism, and Thrombosis with Thrombocytopenia Syndrome for further information.**

Figure 1: Canadian Thrombosis with Thrombocytopenia Syndrome Case Definition (Conceptual diagram)



Appendix A: Decision tree algorithm for case-finding of Thrombocytopenia Thrombosis Syndrome (TTS)

A. Is the platelet count <150 X 10^9/L?

No → **Level 5: NOT a case of TTS**

YES ↓

B. Was presence of thrombosis/thromboembolism confirmed by ≥ 1 of the following (check all that apply)?

- ☐ **Imaging Study**
  - — Ultrasound – Doppler
  - — CT scan – contrast / angiography
  - — Magnetic resonance venography or arteriography
  - — Echocardiogram
  - — Perfusion V/Q scan
  - — Conventional angiography / digital substraction angiography
- ☐ **Surgical procedure** - that confirmed presence of a thrombus (e.g. thrombectomy)
- ☐ **Pathologic examination** – including biopsy or autopsy

YES → **Level 1 (Definite case) TTS**

No ↓

C. Did the clinical presentation suggest one of the specific clinical syndromes below? (check the most appropriate)

NOTE: *the italicized signs/symptoms in brackets after each are suggestive of the syndrome but not an exhaustive list; some but not all of them should be present.* **Diagnosis of the syndrome by a clinical specialist is also acceptable**

- ☐ **Cerebral venous sinus thrombosis / other Cerebral venous thrombosis** *(new onset of unexplained headache, often severe; focal cerebral dysfunction; encephalopathy; seizure)*
- ☐ **Deep vein thrombosis** *(new onset swelling usually but not always in lower extremities; localized swelling accompanied by pain [may be crampy in nature] and tenderness; reddened/discoloured/warm skin; pitting edema)*
- ☐ **Pulmonary thromboembolism** *(sudden onset: shortness of breath[at rest or on exertion], pleuritic chest pain[sudden, intense, sharp, stabbing or burning in nature, made worse by breathing/coughing/sneezing/laughing], cough +/- hemoptysis), tachypnea, tachycardia, arrhythmia, cyanosis, hypotension)*
- ☐ **Intra-abdominal thrombosis.** *(abdominal pain [may be out of proportion to physical exam findings], bloating, nausea, vomiting, diarrhea, bloody stools, ascites, hepatomegaly if hepatic vein location)*
- ☐ **Ischemic Stroke** *(sudden onset of focal neurologic deficits such as difficulty with speech [dysphasia or dysarthria], hemiparesis, ataxic gait abnormal eye movements, facial paresis)*
- ☐ **Myocardial infarction** *(chest pain [often crushing in nature], shortness of breath, arrhythmias including asystole, cyanosis)*

YES ↓

D. Were imaging &/or lab findings supportive of diagnosis of thrombosis / thromboembolism? (Check all that apply)

- ☐ **Chest radiograph**
- ☐ **Echocardiogram**
- ☐ **Computed tomography without contrast**
- ☐ **D-dimer (elevated above upper limit of normal for age)**

YES → **Level 2 (Probable case TTS)**

No → **Level 3 (Possible case TTS)**

Level 4: EXCLUDED: Reported as TTS but insufficient evidence to meet any level of the case

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