COVID-19 Vaccine-Associated Immune Thrombosis and Thrombocytopenia (VITT): Diagnostic Discrepancies and Global Implications

Ali Zidan, BHSc[1] Abdelrahman Noureldin, BHSc[1] Shreya Anil Kumar, BSc[1] Abdelrahman Elsebaie, BHSc[1] Maha Othman, MD, PhD[1,2,3]

[1] Department of Biomedical and Molecular Sciences, School of Medicine, Queen's University, Kingston, Ontario, Canada
[2] Clinical Pathology Department, Faculty of Medicine, Mansoura University, Mansura, Egypt
[3] Department of Nursing, School of Baccalaureate Nursing, St. Lawrence College, Kingston, Ontario, Canada

Address for correspondence Maha Othman, MD, PhD, Department of Biomedical and Molecular Sciences, School of Medicine, Queen's University, Bottrell Hall, 18 Stuart Street, Kingston, Ontario, K7L 3N6, Canada (e-mail: othman@queensu.ca).

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Abstract

Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been reported in association with the coronavirus disease 2019 preventative adenovirus vector-based vaccines ChAdOx1 nCoV-19 (Oxford/AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson) in hundreds of recipients across the globe. VITT is characterized by thrombosis, typically at unusual sites, low fibrinogen, and elevated plasma D-dimer, generally manifesting between 4 and 28 days following vaccination. Detection of anti-platelet factor antibodies using an enzyme-linked immunosorbent assay (ELISA) is often confirmatory. Although several similar principles subside in most diagnostic criteria for VITT, the presentation of a positive ELISA assay, use of expert hematology and neurology opinion, and exclusion of possible VITT cases outside the "standard" 4 to 28-day timeframe have contributed a lack of global standardization for defining VITT. Accordingly, the global and regional incidence of VITT differs according to the diagnostic pathway and case definition used. This has influenced the public perception of VITT's severity and the decision to use adenovirus vector-based vaccines for limiting severe acute respiratory syndrome coronavirus 2 infection. We hereby delineate the recognized pathogenic mechanisms, global incidence, discrepancies in diagnostic criteria, recommended treatments, and global implications to vaccine hesitancy from this coagulopathy.

Keywords
- VITT
- COVID-19
- SARS-CoV-2
- adenoviral vector vaccines

Following its emergence in late December of 2019 in Wuhan, China, the coronavirus disease 2019 (COVID-19) has since rapidly dispersed worldwide, infecting 613 million people and claiming over 6.5 million lives in the process as of September 2022.[1] Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) agent, this highly contagious viral ailment has catastrophically impacted the world's demographics, becoming the most consequential global health crisis/pandemic since the Spanish flu of 1918.[1]

Since the authorization, in early December of 2020, of the first COVID-19 vaccine in the European Union, manufactured by Pfizer-BioNTech (BNT162b2), this and the subsequent

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authorized vaccines generated have sparked much debate regarding their safety, efficacy, and adverse effects.[1] One rare but highly publicized side effect that created considerable discussion was thrombosis with thrombocytopenia syndrome (TTS), or the more widely adopted scientific descriptor of vaccine-induced thrombotic thrombocytopenia (VITT).[1] Since the first reports in April 2021, numerous studies with conflicting data regarding incidence, severity, and pathogenic mechanisms have been published.[2,3] This narrative review aims to summarize the evidence available on VITT diagnosis, mechanisms, global incidence, and risks. We also highlight the global public impact of this knowledge.

COVID-19 Pathologies and Coagulopathy

Coagulopathy and thromboinflammation have been identified as major pathophysiological complications associated with SARS-CoV-2 infection. This process is marked by elevated levels of D-dimer, von Willebrand factor and interleukin (IL)-6.[4] Thromboinflammation (marked by microvascular thrombosis-associated inflammation), is a consequence of vascular endothelial injury that leads to the loss of endothelial and glycocalyx vascular interfaces, thereby triggering many cellular and humoral inflammatory system amplification pathways. This stimulates coagulation pathways, and hampers anticoagulant pathways.[5] Thrombus formation in large vessels and microvasculature of the lungs is a consequence of a multitude of processes that are discussed below but generally comprise stimulated coagulation, endotheliopathy, upregulated innate and adaptive immunity, along with an activated complement system.[6] Experts suggest that activation in coagulation is initially localized in the lung microcirculation but when it expands systemically, it has been called COVID-19-associated coagulopathy. As the patient requires life-saving oxygen support and their condition worsens, they enter the final stage, which may lead to disseminated intravascular coagulation which is much more serious coagulopathy state.[6,7]

Several theories have been proposed for these varying COVID-associated pathologies. Two stand out; the first states that SARS-CoV-2 infects endothelial cells to trigger vascular inflammation and thrombosis as proven by electron microscopy,[8–10] immunohistochemistry,[11,12] and in situ hybridization.[13] Thus, infection impairs the endothelial cell's ability to exert its normal antithrombogenic properties, as viral particles bind to angiotensin-converting enzyme-2 receptors of endothelial cells in blood vessels.[14] A second theory is based on the development of a "cytokine storm" which induces platelet activation and coagulation that leads to thrombosis with subsequent endothelial injury.[15,16] This cytokine storm is evidenced by elevated levels of chemokines (i.e., IL-6, IL-8), C-reactive protein, ferritin, tumor necrosis factor-α, and C-X-C motif chemokine ligand 8.[4,17] However, some experts have suggested that the occurrence of a "cytokine storm" with COVID-19 could be overstated, considering the broad clinical spectrum of this respiratory disease.[15] Additionally, studies have shown that the substantial increase in proinflammatory cytokines is not observed in most cases, and that the rise in injury biomarkers is also considered mild compared to the increase in those with other COVID-19 unrelated cytokine release syndromes.[15] Taken all together, it is more appropriate to believe that the progression of COVID-19 toward a milder "cytokine breeze" phenotype or "cytokine storm" indicative of severe/critical illness will be highly dependent on varying individual factors.[15]

VITT and Pathogenic Mechanisms

Aside from infection-associated coagulopathy, vaccine-associated coagulopathy has now been identified as a further risk during the pandemic. VITT is characterized by thrombosis, which commonly occurs at unusual sites, such as cerebral venous sinuses, splanchnic vein thrombosis thrombocytopenia, low fibrinogen, and elevated D-dimer.[3,18] These events take place in males or females, typically 18 to 79 years old, anywhere between 4 and 48 days following vaccination using an adenovirus-based vaccines such as AstraZeneca/Oxford (ChadOx1 nCov-19) or Janssen/Johnson & Johnson (Ad26.COV2.S).[3] VITT has been considered similar to immune heparin-induced thrombocytopenia (HIT) since there is a typically strong positive enzyme-linked immunosorbent assay (ELISA) result indicating anti-platelet factor 4 (PF4) antibodies even though heparin use is not a feature of VITT.[1] The autoantibodies bind to complexes of PF4, free deoxyribonucleic acid, and coating proteins of adenoviruses via the Fc portion of autoantibodies then onto platelet membranes to trigger activation and aggregation.[19] Following this, prothrombotic molecules are released and thrombin generation is promoted, and PF4 binds to heparin sulfate and chondroitin sulfate on vascular endothelial cells. Seven theories have been proposed recently to explain VITT.[19] However, the knowledge in this area is still developing to delineate the exact mechanism(s) behind VITT.

Incidence of VITT and Key Information

The first reported cases of VITT were described in a Preprint by a German group of researchers led by Dr. Andreas Greinacher in April 2021, where it was originally termed vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), and later formally published in the *New England Journal of Medicine* (NEJM).[2] Further cases from Norway and the United Kingdom were soon reported in June 2021, and the term VITT was used in all three NEJM articles.[20,21] All three studies reported case series with under 25 patients and all patients received the adenovirus-based, AstraZeneca/Oxford vaccine. Following these, a review paper by Favaloro was published that detailed approximately 100 cases that had been described in literature as of May 2021, and these were also all associated with the use of adenovirus vaccines AstraZeneca and Johnson & Johnson.[22] Since then additional literature has been published. Currently, the estimates for risk of VITT and incidence vary dramatically in literature; however, it is agreed that this is a very rare adverse effect of adenovirus-based vaccines. One review paper published in February 2022 highlights that incidence ranges between 1/26,000 and

1/1,273,000, and no clear risk factors could be identified among sex, age, or comorbidities.[23] A correspondence in September 2022 in NEJM estimates the incidence of VITT between 3.2 and 16.1 manifestations per million for the Oxford/AstraZeneca vaccine and 1.7 and 3.7 per million doses of the Johnson & Johnson vaccine.[24] Although the Sputnik V vaccine has been suggested to be a potentially potent cause of VITT, the recognized incidence may be undervalued given its lack of reporting in global literature.[25] Yet, Argentina, a large consumer of the vaccine, recently confirmed two cases of VITT after 20,538,979 doses were administered, verifying reported incidence.[24]

Prevalence of VITT will differ according to the case definition and diagnostic pathway chosen. Only 58 cases of TTS worldwide were identified by a systematic review in August of 2021 based on World Health Organization criteria; however, the study by Favaloro published earlier in June 2021 documented at least 100 cases by an earlier date of May.[22,26] This discrepancy can be attributed to differential diagnoses of vaccine-induced thrombotic complications.[27] Although the original term reported was VIPIT, VITT has since been used and reflecting variation in the abbreviation HITT (heparin-induced thrombocytopenia with thrombosis), both show several similarities in pathophysiology.[22] Vaccine-associated immune thrombotic thrombocytopenia was another term supported by researchers concerned with the terminology including the word "induced," since a pathological link to the vaccine was not actually clear.[22] Finally, the descriptor TTS has also been used, mainly by government reporting agencies, perhaps fearful of highlighting any vaccine association.[22]

The highest individual incidence based on country has been reported in Norway, where five cases occurred among 130,000 individuals vaccinated with ChAdOx1 nCoV-19, suggesting an incidence of 1 in 26,000 for VITT (not TTS).[21] On the other hand, a January report from the Vaccine Adverse Event Reporting System surveillance system to the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration identified approximately 50 cases among over 14 million recipients of Ad26.COV2.S, for an incidence of 1 in 263,000.[28] However, incidence rates will vary based on diagnostic definitions and geographic location, including country resources and surveillance abilities. For example, the first state in Australia to identify a VITT case may have be most attuned to the possibility of VITT postvaccination, and thus, more proactive in data collection.[3] Further, Australia is one of several countries that has since mitigated AstraZeneca use, among other adenovirus-based vaccines, and thus their incidence of VITT was disproportionately lower or not even reported on.[29] However, most recently, they reported data from a large multicenter study evaluating anti-PF4 testing. The study showed discrepancies in test results, highlighted the limitations of relying on a single method, and demonstrated the variability in phenotypes and pathomechanism of VITT.[30] Countries which have previously suspended the AstraZeneca COVID-19 vaccine include Denmark, Sweden, Italy, and Norway, among others.[31] ►**Table 1** lists confirmed cases of VITT based on vaccine type.

Diagnostic Criteria and Guidelines

The criteria for diagnosing and reporting VITT has largely been influenced by local guidelines, regionally reported cases, and their respective clinical environments.[32] At least 10 diagnostic criteria for possible VITT have been identified, mainly originating from the United Kingdom, North America, Australia, and health care organizations in mainland Europe.[3] This includes the National Institute for Health and Care Excellence from England, the Spanish Federation of Medical and Scientific Associations for VITT manifesting as cerebral venous sinus thrombosis, and Italian Society for the Study of Haemostasis and Thrombosis.[33–35] Other criteria include that of the American Society of Haematology, International Society on Thrombosis and Haemostasis

Table 1 Confirmed cases of VITT based on vaccine type and manufacturer

Vaccine type	Vaccine name	Confirmed VITT
Recombinant protein subunit	Covovax (Novavax Formulation, Serum Institute of India)	No
Recombinant protein subunit	Nuvaxovid (Novavax)	No
mRNA	Spikevax (Moderna)	No
mRNA	Comirnaty (Pfizer/BioNtech)	No
Non-replicating viral vector (adenovirus)	Convidecia (CanSino)	No
Non-replicating viral vector (adenovirus)	Janssen (Janssen [Johnson & Johnson])	Yes[22,28]
Non-replicating viral vector (adenovirus)	Vaxzevria (Oxford/AstraZeneca)	Yes[2,20–22]
Non-replicating viral vector (adenovirus)	Sputnik V (Gamaleya)	Yes[24]
Inactivated virus	Covaxin (Bharat Biotech)	No
Inactivated virus	Covilo (Sinopharm)	No
Inactivated virus	CoronaVac (Sinovac)	No
Plant-based recombinant, protein virus-like particle	Covifenz (Medicago)	No

Abbreviations: mRNA, messenger ribonucleic acid; VITT, vaccine-induced thrombotic thrombocytopenia.

(ISTH), American Heart Association, Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ), and that of the Ontario COVID-19 Science Advisory Table.[1,36–39]

Cumulatively, a few basic tenets subside in most criteria, including elevated D-dimer ($>$ 4,000 µg/mL [fibrinogen equivalent units]), reduced fibrinogen (below the normal range), positive anti-PF4 antibodies by ELISA testing, thrombocytopenia (platelet count $< 150 \times 10^9$/L), and an onset of symptoms after 4 days of adenovirus-based COVID vaccination.[40,41] Conversely, each criterion contains slight variations, mainly due to the timing of their release, influence of research based on newly reported cases, and whether they have been updated routinely.[3,32]

Exemplarily was the exclusion of possible VITT cases outside of the 28-day, postvaccination period, which is now believed to be limiting to identification of prior potential cases.[3] The ISTH and Ontario COVID-19 Science Advisory Table both used a 4 to 28-day timeframe when publishing their criteria in April and May of 2021, respectively.[1,37] Contrarily, the recent version for diagnosing VITT by the American Society of Hematology and THANZ use an inclusion criterion of 4 to 42 days, updated in May 2022 and December 2021, respectively, displaying the progression of understanding developed by the international community, as well as the cases attained in those localities.[3,30,36,39]

The use of ELISA assays for detecting anti-PF4 antibodies has thus far been largely accepted to confirm VITT.[40,41] In terms of reporting, however, this criterion is not yet extensively indispensable. For example, negative or obscure results for ELISA have been used in several cases.[42,43] In Scully et al's publication in June 2021, an individual with elevated D-dimer, low fibrinogen, and deep venous thrombosis and bilateral adrenal hemorrhage had an ambiguous ELISA level of 0.156 optical density on the Asserachrom HPIA IgG assay.[20] Likewise, a clinically indistinguishable individual tested negative on ELISA (Lifecodes PF4 IgG assay) and functional HIT assay.[20] More recently up to 1/3 of VITT cases identified using functional assays to be ELISA negative by Asserachrom assay in a large Australian multicenter study with 1,284 patients.[30]

Another criterion for confirming VITT by some studies was the use of expert opinion in neurology and hematology, further emphasizing the lack of standardization.[32]

Guidance on Treatment

Treatment for VITT has been outlined by several national and international societies, including the CDC, ISTH, and American Society of Hematology, among others. Generally, any patient with cerebral venous sinuses thrombosis (CVST) should be transferred to a center with capabilities for neurosurgical intervention.[44] To avoid further complications, anticoagulation therapy is required; however, low molecular weight heparin is not recommended as this may worsen conditions.[44] Nonheparin anticoagulants such as apixaban, rivaroxaban, and direct thrombin inhibitors such as argatroban are preferred.[44] In CVST particularly, parenteral agents are preferred, while oral alternatives can be considered after the acute phase or at discharge. Anticoagulation should also continue for at least 3 months after platelet counts have normalized.[44]

Intravenous immunoglobulin (IVIG) is the only available therapy that can interfere with anti-PF4 antibodies and limit VITT progression, and high doses are required (1 g/kg/day).[45] Furthermore, if IVIG is not available, steroids may be considered, such as prednisone at 1 to 2 mg/kg/day, to mitigate the immune response.[45] Platelet transfusions should also generally be avoided; however, this may be considered where life-threatening bleeding occurs or immediate major surgery is needed.[45] A list of expert group guidelines with details on treatment is provided in ►**Table 2**.

Global Implications of VITT

In response to growing knowledge on VITT and its implications, countries such as the Philippines and Portugal have taken preventative measures to protect their populations. Namely, they suspended the use of the AstraZeneca vaccine to residents under 60 years old in April and May of 2021, respectively.[46,47] In the Philippines, this suspension lasted for under 2 weeks, but may have catalyzed the growing vaccine hesitancy nationwide, as almost half of residents

Table 2 Expert guidelines on treatment of VITT

Society	Guidelines
American Society of Hematology (ASH)	https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia
International Society on Thrombosis and Haemostasis (ISTH)	https://www.isth.org/news/561406/
American College of Cardiology (ACC)	https://www.acc.org/latest-in-cardiology/articles/2021/04/01/01/42/vaccine-induced-thrombotic-thrombocytopenia-vitt-and-covid-19-vaccines
American Heart Association/American Stroke Association	https://www.ahajournals.org/doi/10.1161/STROKEAHA.121.035564
National Institute for Health and Care Excellence (NICE) in the United Kingdom	https://www.nice.org.uk/guidance/ng200

Abbreviation: VITT, vaccine-induced thrombotic thrombocytopenia.

were unwilling or unsure of pursing COVID-19-associated vaccine based on a series of nationwide surveys in September 2021.[48] On the other hand, Brazil, a nation with one of the lowest vaccine hesitancy rates (9.8% in June 2021) in comparison to the global average of 24.8% at this time, experienced a different conjuncture.[49] As their governing health care body worked with the ISTH and were made aware of VITT's progression, the AstraZeneca vaccine was not restricted during this time, and only in May for pregnant women.[50] That said, vaccine hesitancy continued to remain consistent to previous levels, as the developing nation continued purchasing AstraZeneca vaccines—what was believed to be the best cost–benefit acquisition in the country based on a simulation in August of 2021.[51] In the United Kingdom, it was concluded by the Joint Committee on Vaccination and Immunization in May 2021 that adults under 40 should be offered an alternative to the AstraZeneca vaccine only if it does not cause significant delays in vaccination rates.[52] In conjunction with the suspension of this vaccine by Germany, France, and Denmark during this time, it was presumably developing nations who suffered most from this hesitancy.[53] The Democratic Republic of Congo and Cameroon for instance began delaying injections of their modest supply of this vaccine, which experts suggest, would cost many lives if hesitancy persisted.[53] The authors are aware of several groups around the world conducting VITT-related research to improve the understanding of the pathophysiology and/or investigating the potential of a safer vaccine in collaboration with AstraZeneca.

Concluding Remarks

VITT remains a very rare side effect to—so far—only adenoviral-based COVID-19 vaccine. National reactions to VITT varied across the globe between pausing, suspending completely, and continuing to offer those types of vaccines based on cost–benefit value. The diagnosis and management of VITT have largely been influenced by the local guidelines, the regionally reported cases, and their respective clinical environments. At least 10 diagnostic guidelines currently exist, and a global collaborative effort has led to the identification of the basic underlying mechanism involving anti-PF4 antibodies. The use of ELISA assays for detecting anti-PF4 antibodies has been largely accepted to confirm VITT diagnosis. However, there are discrepancies in test results between various assay types. This may reflect the variability in phenotypes and/or mechanisms of VITT in different individuals. Research will continue on VITT and is expected to reveal more in the future about the complex pathophysiology of this rare but serious condition.

Conflict of Interest
None declared.

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