COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A review of the potential mechanisms and proposed management

Walid Alam
Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

Abstract
With over 600 million coronavirus (COVID-19) vaccine doses administered globally, adverse events are constantly monitored. Recently however, reports of thrombosis and thrombocytopenia following vaccination with the ChAdOx1 nCoV-19 vaccine have emerged. This paper aims to review the available literature and guidelines pertaining to vaccine-induced immune thrombotic thrombocytopenia (VITT) and the proposed guidelines, while offering a potential approach that unifies the available evidence. While the risk of VITT remains extremely low and the benefits outweigh the risks, experimental studies are needed to clarify the pathophysiology behind VITT and possibly decrease the risk of thrombosis and other adverse events occurring. However, treatment should not be delayed in suspected cases, and IV immunoglobulin and non-heparin anticoagulation should be initiated.

Keywords
Vaccine-induced immune thrombotic thrombocytopenia, COVID-19, VITT, vaccine-induced pro-thrombotic immune thrombocytopenia, VIPIT, thrombosis, thrombocytopenia, ChAdOx1 nCoV-19, thrombosis with thrombocytopenia syndrome, TTS

Introduction
As of April 7, 2021, over 669 million coronavirus (COVID-19) vaccine doses have been administered globally.\(^1\) To date, the European Medicines Agency (EMA) has authorized the use of four vaccines: Comirnaty (Pfizer/Biontech), COVID-19

Corresponding author:
Walid Alam, MD, Global Health Institute (GHI), American University of Beirut, Gefinor Center, Third Floor, Clemenceau Street, Beirut 1107 2020, Lebanon.
Email: alamwalid94@gmail.com
Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Vaccine Janssen (Johnson and Johnson’s), Moderna, and Vaxzveria (AstraZeneca). The ChAdOx1 nCoV-19 vaccine (AstraZeneca/Vaxzveria) is a recombinant chimpanzee adenoviral vector encoding the spike glycoprotein of SARS-CoV-2, that was found to have a good efficacy rate and an adequate safety profile. However, over the past 2 months concern has been raised over reported thrombotic events associated with thrombocytopenia after the use of the AstraZeneca vaccine, a complication called vaccine-induced immune thrombotic thrombocytopenia (VITT) or vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). The University of Cambridge’s Winton Centre for Risk and Evidence Communication analyzed the potential benefits and harm of the vaccine and found that the risk of clot is around 1:250 000 in the general population but higher in younger people (20–29 years old) at 1.1:100 000. While the Medicines and Healthcare products Regulatory Agency (MHRA) concluded that there is a possible link between the Astrazeneca vaccine and thrombotic events, it still recommends the use of the vaccine as the benefits far outweigh the risks.

The mechanism by which VITT occurs is still uncertain but similarities with heparin induced thrombocytopenia (HIT) and spontaneous HIT syndrome have been suggested. This review aims to evaluate the current proposed mechanisms as well as provide a potential approach to diagnosis and management.

Methods

Electronic database searches were carried out in Medline, PubMed, Embase, Google Scholar with the period set from January 1, 2021 to April 10, 2021. The search process was focused on case reports, reviews, trials, and original articles where the ChAdOx1 nCoV-19 vaccine was evaluated for adverse events. Keywords included “COVID-19,” “vaccine,” “ChAdOx1 nCoV-19,” “AstraZeneca,” “Vaxzveria,” “thrombosis,” “clot,” “adverse events,” “Vaccine-Induced Immune Thrombotic Thrombocytopenia,” “VITT,” “Vaccine induced Prothrombotic Immune Thrombocytopenia,” “VIPIT” as exact phrases, and a combination of subject headings according to databases syntax. The references listed in each identified article were also screened and manually searched. No language restrictions were imposed in any of the searches. Additionally, another search was conducted with the keywords: “heparin induced thrombocytopenia,” “HIT,” “platelet factor 4,” “PF4,” and “spontaneous HIT syndrome.”

Discussion

Overview of heparin Induced thrombocytopenia and spontaneous HIT syndrome

Two types of HIT are described: Type I and Type II. Type I HIT is mediated by a direct interaction between heparin and circulating platelets causing platelet clumping or sequestration and does not involve an immunologic reaction. It presents within 48–72 h of treatment, is self-resolving, and is not associated with increased
risk of thrombosis. Type II HIT, however, is immune mediated, leads to an increased risk of thrombosis, and thrombocytopenia typically occurs 5–10 days after initiation of heparin.\textsuperscript{8} In short, type II HIT is an immune mediated adverse reaction caused by the emergence of antibodies that activate platelets in the presence of heparin. Polyanionic heparin binds to cationic platelet factor 4 (PF4), a molecule found in the \(\alpha\)-granules of platelets, forming a complex that leads to the generation of heparin–PF4 antibodies (HIT antibodies). A multimolecular immune complex formed of heparin–PF4–IgG binds to Fc\(\gamma\)IIa receptors found on platelets, thereby activating them, and leading to the release of prothrombotic platelet-derived microparticles, platelet consumption, and thrombocytopenia. This in turn favors thrombosis through the generation of excessive thrombin. The complex can also promote the activation of the coagulation cascade and thrombin generation through its interaction with monocytes which produce tissue factor, and through an antibody-mediated endothelial injury (Figure 1).\textsuperscript{9} HIT is usually managed by immediately stopping heparin and monitoring platelet counts and thrombotic events while also switching to non-heparin anticoagulants.\textsuperscript{8,9} Alternatives include direct thrombin inhibitors, fondaparinux, or direct oral anticoagulants (DOACs). The choice of anticoagulant depends on the clinical scenario as the American Society of Hematology (ASH) highlighted in its 2018 guidelines and recommendations. For example, the ASH recommends the use of bivalirudin over other non-heparin anticoagulants in patients with HIT who require percutaneous coronary intervention (PCI).\textsuperscript{10}

A clinical entity similar to HIT has been identified over the last few years, one that presents with identical characteristics such as thrombocytopenia, thrombosis, and detectable HIT antibodies with the difference being that platelets are activated through a heparin-independent process. This entity is named “spontaneous HIT syndrome” and is classified under the umbrella of “autoimmune heparin-induced thrombocytopenia (aHIT) syndromes.”\textsuperscript{11,12} Several triggers of spontaneous HIT syndrome have been identified and include viral infections that led to cerebral venous sinus thrombosis (CVST),\textsuperscript{12} and thrombocytopenia and thrombosis following infectious or inflammatory events.\textsuperscript{13} Surgical procedures have also been linked to spontaneous HIT, with a recent case of CVST reported post knee arthroplasty, possibly connected to the release of knee cartilage glycosaminoglycans or RNA from tourniquet related cell ischemia.\textsuperscript{14} Other polyanionic drugs have also been found to trigger HIT including the antiangiogenic agent PI-88, polysulfate, and hypersulfated chondroitin sulfate.\textsuperscript{15,16} Nevertheless, aHIT syndromes are characterized by a more severe form of thrombocytopenia than observed in classic HIT, an increased frequency of disseminated intravascular coagulation (DIC), and atypical thrombotic events.\textsuperscript{11} Spontaneous HIT syndrome is diagnosed based on several criteria proposed in 2014 (Table 1).\textsuperscript{17} However, some of these criteria require referral to specialized laboratory that are able to carry out serological studies on the serum (platelet serotonin-release assay (SRA) or another functional assay such as the heparin-induced platelet activation test) but management of suspected spontaneous HIT should not be delayed. Serotonin is found in the dense granules of...
platelets, and measurement of the percentage of its release can be used to quantify the magnitude of platelet activation induced by a variety of platelet agonists, including HIT antibodies within patient serum or plasma. In spontaneous HIT...
syndrome, SRA is strongly positive with peak serotonin release found to be at >80% at 0.1–0.3 U/mL heparin along with strong heparin-independent platelet activation seen where serotonin release is found to be at >50% in the absence of heparin (0 U/mL). Currently, PF4 dependent ELISA assays are done either as screening before SRA or as an adjunct to SRA to reduce the risk of a false-positive SRA. At least two distinct positive PF4-dependent ELISA assays are required for diagnosis of spontaneous HIT, and the combination of ELISA and SRA is essential to prevent overdiagnosis. Additional characteristics of the syndrome include inhibition of reactivity at high heparin concentrations (100 U/mL) and of platelet activation by Fc receptor blockade. Concerning treatment, evidence suggests that the use of high dose intravenous immunoglobulin (IVIg) to block the platelet IgG receptor, FcγRIIa, has a favorable clinical outcome.

**Vaccine-induced immune thrombotic thrombocytopenia**

The German Society of Thrombosis and Haemostasis (GTH) found that out of approximately 2.2 million AstraZeneca COVID-19 vaccine doses that had been administered, a total of 31 cases of sinus or cerebral vein thrombosis had been reported to the Paul Ehrlich Institute (PEI). The thromboses occurred 4–16 days post vaccination and concomitant thrombocytopenia was reported in 19 patients, with the clinical course fatal in nine patients. Reported cases included 29 women aged 20–63 years and two men aged 36 and 57 years. A mechanism similar to HIT was demonstrated in four patients where antibodies were found to cause massive platelet activation via the Fc receptor. Two case series were published describing patients with VITT. The article by Schultz et al. described five healthcare workers aged 32–54 years who presented with severe venous thromboembolism at unusual sites (portal vein, transverse and sigmoid sinuses, deep and superficial cerebral veins), and concomitant thrombocytopenia ranging from 10,000 to 70,000/mm³, that occurred 7–10 days after vaccination with ChAdOx1 nCoV-19. All five patients had elevated D-dimer levels and high levels of IgG antibodies to PF4–polyanion complexes as measured by ELISA and demonstrated

### Table 1. Diagnostic criteria for spontaneous HIT syndrome.

| Spontaneous HIT syndrome diagnostic criteria |
|---------------------------------------------|
| Thrombocytopenia (platelet count < 150 × 10⁹/L) |
| Thrombosis                                   |
| Absence of proximate heparin exposure       |
| Positive PF4-dependent ELISA assays (≥2 distinct assays) |
| Strongly positive SRA (>80% peak serotonin-release) featuring heparin-independent platelet activation (>50% release at 0 IU/mL heparin) |
| Heparin-dependent platelet activation on sample dilution |
| Lack of serotonin release at 100 U/mL heparin and with platelet Fc receptor-blocking monoclonal antibody |
platelet activation in the absence of heparin. Fibrinogen levels were predominantly normal to borderline low. Treatment with IVIg and prednisolone was initiated and led to an increase in platelet counts, while low-molecular-weight heparin (LMWH) was continued but did not affect platelet counts nor increase bleeding risk. In the paper by Greinacher et al., 11 patients, aged 22–49 years, had one or more thrombotic complications 5–16 days post vaccination. Nine patients developed cerebral venous thrombosis, three developed splanchnic-vein thrombosis, three developed pulmonary embolism, and four developed other types of thrombi which included thrombosis in the aortoiliac and the iliofemoral veins, the inferior vena cava (IVC), and the right intraventricular cavity. All patients had concurrent thrombocytopenia with the platelet count ranging from 9000 to 107,000/mm³. Of the seven patients tested for d-dimers, all had elevated levels ranging from 1.8 to 142 mg/L (reference value ≤0.5 mg/L). Five of these patients also had reduced fibrinogen levels. Serological testing for all patients was positive for antibodies against PF4–heparin and testing with the platelet-activation assay was also positive in the presence of PF4 independent of heparin. The authors recommend treating suspected cases of VITT with high dose IVIg (1 g/kg for 2 days) and using non-heparin anticoagulation (e.g. direct oral Xa inhibitors, direct thrombin inhibitors, fondaparinux). Though detection of PF4-heparin antibodies by ELISA and a positive platelet-activation assay (preferably a PF4-dependent assay) are required to confirm diagnosis, treatment should not be delayed.

Concerning the mechanism by which immune thrombotic thrombocytopenia (ITT) is triggered by the ChAdOx1 nCoV-19 vaccine, the primary hypothesis relates to the reaction between the cationic PF4, and the anionic free DNA found in the recombinant adenovirus vaccine. A 2013 study demonstrated in a murine model that DNA and RNA form multimolecular complexes with PF4 and expose the epitope to which anti-PF4/heparin antibodies bind, while also inducing an immune response resembling HIT.

Several medical societies have released their own guidelines on how to approach VITT. Based on these guidelines and the above case series, we can propose the following criteria to diagnose VITT (Table 2). The criteria suggestive of VITT are the onset of symptoms within 4–24 days post vaccination, thrombocytopenia, and markedly elevated d-dimer levels. This should prompt further investigation for VITT and rapid assessment of the need for initiation of treatment. All patients presenting with signs and symptoms suggestive of thrombosis and/or thrombocytopenia 4–28 days after COVID-19 vaccination should have a full blood count (FBC) ordered along with coagulation studies. Flu-like symptoms such as headache or myalgia and arthralgias that persist for 1–2 days after vaccination are a common side effect. As most cases of VITT have been found to present with thrombosis in the cerebral venous system and the splanchnic-veins, imaging should be guided based on clinical presentation. For example, in a patient presenting with severe persistent headache, an urgent brain CT without contrast should be done to identify signs of CVST (infarct, hemorrhage, and edema). If the risk is assessed to be intermediate to high, follow-up imaging with cerebral venography can be done.
Concerning coagulation studies, d-dimer levels have been found to be highly elevated in VITT often reaching five times the upper normal limit (UNL), while fibrinogen levels are reduced but can also be normal. The combination of thrombocytopenia and elevated d-dimers can be considered as sufficient criteria to diagnose probable VITT. All patients with suspected VITT should be screened for PF4-heparin antibodies using PF4-heparin (HIT) ELISA, and if positive, a sample should be sent for testing with a platelet activation test (PAT). Widely available PATs include SRA and the classical heparin-induced platelet activation (HIPA) assay. While ELISA and PAT are required for confirmation of diagnosis, treatment should not be delayed. A proposed approach to the definitive diagnosis of VITT could therefore include the fulfillment of the following criteria: vaccination 4–28 days prior to presentation, thrombocytopenia, markedly elevated d-dimer levels, and positive HIT ELISA and PAT. As previously mentioned, initial imaging may not show thrombosis in all cases of VITT, and fibrinogen levels may be normal.

Regarding treatment, high dose IVIg (1 g/kg for 2 days) should be administered urgently when suspecting VITT as it inhibits the action of platelet activating anti-PF4 antibodies by blocking platelet Fc receptors and has been found to increase platelet count while decreasing hypercoagulability in aHIT. For anticoagulation, non-heparin anticoagulants should be used, and these include direct oral Xa inhibitors (DOACs), direct thrombin inhibitors, and fondaparinux. The similarities between VITT and HIT/aHIT have led to recommendations against the use of unfractionated or LMWH in patients with suspected VITT. However, the effects of giving heparin to patients with VITT are still unclear with some evidence suggesting heparin could actually inhibit platelet activation mediated by VITT antibodies. In patients who received IVIg and prednisolone, platelet counts increased despite continuing treatment with low-molecular-weight heparin. Similarly, serum samples of patients with VITT were tested and it was found that platelet activation was inhibited by LMWH and strongly enhanced in the presence of PF4. However, high levels of unfractionated heparin inhibited the reaction in all but one serum

### Table 2. Summary of the criteria used to diagnose vaccine-induced immune thrombotic thrombocytopenia (VITT). Thrombocytopenia and very elevated d-dimers are suggestive of VITT and should prompt further investigation with the above tests and imaging. Positive ELISA and positive PAT are required for definitive diagnosis.

| Criteria                        | Details                                                                 |
|---------------------------------|-------------------------------------------------------------------------|
| Onset of symptoms               | 4–28 days post vaccination                                              |
| Platelet count                  | < 150 × 10^9/L                                                          |
| d-dimers                        | 5 × upper normal limit                                                  |
| Imaging                         | Atypical thrombosis (cerebral venous sinus, portal vein)                |
| Fibrinogen                      | Reduced                                                                 |
| HIT ELISA                       | PF4-heparin antibodies                                                  |
| Platelet activation test (PAT)  | Platelet activation independent of heparin                              |
A team at the University of Birmingham published the results of their study, in preprint, which investigated the effects of serum from patients with VITT on platelet aggregation and assessed the utility of clinically available drugs in preventing platelet activation. The authors found that both low (0.1 and 0.3 U/ml) and high (100 U/ml) concentrations of heparin blocked in vitro platelet aggregation in serum samples obtained from patients with VITT. Nevertheless, the evidence is still lacking, and more studies are needed to evaluate the role of heparin in VITT as non-heparin anticoagulants carry a major bleeding risk and can be problematic in certain clinical scenarios.

In the absence of thrombosis, prophylactic anticoagulation should be initiated while therapeutic anticoagulation is given in the presence of thrombosis. Importantly, platelet transfusion is contraindicated unless undergoing invasive procedure with high risk of bleeding, such as neurosurgery, in which case transfusion should target a platelet count of \( >100 \times 10^9/L \).

An overview of the management of VITT combining the above recommendations is depicted in the figure below (Figure 2). Patients without thrombocytopenia are unlikely to have VITT, however coagulation studies can help to further rule out the disease. Other causes should be pursued, and imaging can be used in case of persistent symptoms, for example, headache, shortness of breath, abdominal pain. In patients whose platelet count ranges between 100 and \( 150 \times 10^9/L \), VITT cannot be excluded and further investigation with coagulation studies and repeat blood count are advised. Imaging is reserved in case of high suspicion of thrombosis due to persistent severe symptoms. In patients with severe thrombocytopenia \( (<100 \times 10^9/L) \) and an elevated d-dimer or reduced fibrinogen, imaging is recommended to rule out thrombosis. However, patients should be started on high dose IVIg (1 g/kg for 2 days) regardless of thrombosis status with anticoagulation protocol tailored toward imaging results. Screening is usually done by HIT ELISA and confirmation requires both ELISA and PAT testing with a positive result in both necessitating continued anticoagulation, while a negative ELISA requires monitoring of platelet counts and a repeat of ELISA after a few days. VITT is still possible if ELISA is positive but PAT is negative requiring repeat testing and management based on symptomatology/clinical course and suspicion. Other commercially available non-ELISA assays were also evaluated for their ability to identify anti-PF4 antibodies in samples taken from patients with suspected VITT. A recent study done by Platton et al. in the UK, evaluated the use of four IgG-specific ELISA assays, two polyspecific ELISA assays, and four non-ELISA rapid assays on 43 samples taken from patients with suspected VITT. The authors found that the rapid assays, HemosIL AcuStar HIT-IgG, HemosIL HIT-Ab, Diamed PaGIA gel, and STic Expert had poor sensitivity for anti-PF4 antibodies in comparison to ELISA and were unreliable for the screening of VITT. Additionally, the study found no significant difference in sensitivity between IgG-ELISA assays and polyspecific ELISA assays, though it is important to note that no single ELISA method detected all suspected VITT cases leading the authors to recommend the usage of a second ELISA or a platelet activation assay when clinical suspicion for VITT is
**Sign and Symptoms** suggestive of thrombosis and/or thrombocytopenia 4-28 days post COVID-19 vaccination

- **Platelet counts >150x10^9/L**
  - Normal D-dimer levels and fibrinogen
  - VITT very unlikely

- **Platelet counts <100x10^9/L + elevated d-dimers or reduced fibrinogen**
  - VITT suspected

- **Platelet counts between 100-150x10^9/L**
  - Imaging depending on clinical picture

- **Platelet counts <100x10^9/L + elevated d-dimers or reduced fibrinogen**
  - Imaging depending on clinical picture
  - VITT not excluded: coagulation studies + re-evaluate and repeat testing

- **Investigate other causes. Consider imaging in case of persistent symptoms (e.g., non-contrast CT brain for persistent headache).**

- **Thrombosis found**
  - Probable VITT: urgent IV Ig + non-heparin therapeutic anticoagulation

- **No thrombosis**
  - Possible VITT: urgent IV Ig + consider non-heparin prophylactic anticoagulation

- **Next steps in management depend on laboratory confirmation of VITT**

**Figure 2.** Potential strategy for the diagnosis and management of vaccine-induced immune thrombotic thrombocytopenia (VITT).

PAT: platelet activation test; the most commonly available is the platelet serotonin-release assay (SRA); however, a PF4-dependent assay is more specific.

*Management should be started before serology results.*
On the other hand, a team from the University Medicine Greifswald developed and evaluated the use of a rapid assay to diagnose VITT. The assay known as PIFPA (PF4-induced flow cytometry-based platelet activation) is a whole blood standard flow cytometric assay and is based on a washed platelet assay, the PF4-induced platelet activation test (PIPA), which is a modified functional heparin-induced platelet activation test that has high specificity to the ChAdOx1 nCov-19 vaccine-related antibodies but is only found in specialized labs. The study found that the PIFPA test had very comparable results to the PIPA test and can be used to detect anti-PF4 antibodies. However, the authors concede that some patients with VITT might have weakly reacting antibodies that might not be detected with PIFPA and may require testing with PIPA. Nevertheless, further studies are needed to replicate the study’s findings, but successful implementation of this assay could provide a widely applicable tool to rapidly diagnose VITT in labs with limited resources and that lack access to platelet activation assays.

Limitations

This review discusses a recent complication that is still poorly understood. As such, the mechanism of the pathophysiology is still unclear beyond a general hypothesis, and the management and diagnosis are still evolving with different bodies proposing their own algorithms. Additionally, while the cases described here are linked to the AstraZeneca vaccine, reports of thrombosis with the use of the Johnson and Johnson’s vaccine are emerging and VITT could potentially be observed with other vaccines as an increasing number of people become vaccinated. An experimental study needs to be undertaken to demonstrate the mechanism by which certain COVID-19 vaccines can cause a syndrome similar to HIT. Finally, the proposed algorithm in this paper is merely a collection of different guidelines refined to include all the recommendations, but as information regarding VITT is rapidly evolving, some recommendations are bound to change.

Conclusion

With the recent administration of millions of doses of different vaccine types against COVID-19 after emergency approval, the development of serious adverse events is carefully monitored globally. However, the recent emergence of a syndrome mimicking HIT after vaccination has raised a few alarms with several medical societies providing recommendations on diagnosis and management of this syndrome known as VITT/VIPIT that has also been recently termed thrombosis with thrombocytopenia syndrome (TTS). Keeping in mind that the risk of VITT remains extremely low and the benefits outweigh the risks, experimental studies are needed to clarify the pathophysiology behind VITT and possibly decrease the risk of thrombosis and other adverse events occurring. In any case, patients presenting with signs and/or symptoms of thrombosis and found to have thrombocytopenia within 4–28 days post vaccination for COVID-19, should be carefully evaluated for...
the possibility of VITT. Currently, the PF4-heparin (polyanion) ELISA assay remains the best screening tool while other non-ELISA tests have limited sensitivity and clinical utility in detecting VITT related antibodies. A promising new assay, the PIPFA test, could serve as an alternative to platelet assays, is more widely available, is highly specific to VITT related antibodies, and has been shown to allow for rapid diagnosis of VITT. However, additional studies are still needed to replicate these findings.

Author’s note
Walid Alam is currently affiliated with Global Health Institute (GHI), American University of Beirut, Hamra, Lebanon.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Walid Alam https://orcid.org/0000-0002-3714-6674

References
1. World Health Organization. WHO coronavirus (COVID-19) dashboard, https://covid19.who.int/ (accessed 10 April 2021).
2. European Medicines Agency. COVID-19 vaccines: authorised, https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised (accessed 7 April 2021).
3. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK [published correction appears in Lancet. 2021; 397(10269): 98]. Lancet 2021; 397(10269): 99–111.
4. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. Epub ahead of print 9 April 2021. DOI: 10.1056/NEJMoa2104840.
5. Schultz NH, Sørvell IH, Michelsen AE, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med. Epub ahead of print 9 April 2021. DOI: 10.1056/NEJMoa2104882.
6. Winton Centre for Risk and Evidence Communication. Communicating the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine, https://wintoncentre.
7. Medicines and Healthcare products Regulatory Agency. MHRA issues new advice, concluding a possible link between COVID-19 Vaccine AstraZeneca and extremely rare, unlikely to occur blood clots, https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots (2021, accessed 7 April 2021).

8. Ahmed I, Majeed A and Powell R. Heparin induced thrombocytopenia: diagnosis and management update. *Postgrad Med J* 2007; 83(983): 575–582.

9. Arepally GM. Heparin-induced thrombocytopenia. *Blood* 2017; 129(21): 2864–2872.

10. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv* 2018; 2(22): 3360–3392.

11. Greinacher A, Selleng K and Warkentin TE. Autoimmune heparin-induced thrombocytopenia. *J Thromb Haemost* 2017; 15(11): 2099–2114.

12. Moores G, Warkentin TE, Farooqi MAM, et al. Spontaneous heparin-induced thrombocytopenia presenting as cerebral venous sinus thrombosis. *Neurrol Clin Pract*. Epub ahead of print 14 January 2020. DOI: 10.1212/cpj.0000000000000805.

13. Warkentin TE, Makris M, Jay RM, et al. A spontaneous prothrombotic disorder resembling heparin-induced thrombocytopenia. *Am J Med* 2008; 121: 632–636.

14. Hwang SR, Wang Y, Weil EL, et al. Cerebral venous sinus thrombosis associated with spontaneous heparin-induced thrombocytopenia syndrome after total knee arthroplasty. *Platelets*. Epub ahead of print 1 October 2020. DOI: 10.1080/09537104.2020.1828574.

15. Tardy-Poncet B, Tardy B, Grelac F, et al. Pentosan polysulfate-induced thrombocytopenia and thrombosis. *Am J Hematol* 1994; 45(3): 252–257.

16. Rosenthal MA, Rischin D, McArthur G, et al. Treatment with the novel anti-angiogenic agent PI-88 is associated with immune-mediated thrombocytopenia. *Ann Oncol* 2002; 13(5): 770–776.

17. Warkentin TE, Basciano PA, Knopman J, et al. Spontaneous heparin-induced thrombocytopenia syndrome: 2 new cases and a proposal for defining this disorder. *Blood* 2014; 123(23): 3651–3654.

18. Warkentin TE, Arnold DM, Nazi I, et al. The platelet serotonin-release assay. *Am J Hematol* 2015; 90(6): 564–572.

19. Oldenburg J, Klamroth R, Langer F, et al. Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: guidance statement from the GTH. *Hamostaseologie*. Epub ahead of print 1 April 2021. DOI: 10.1055/a-1469-7481.

20. Jaax ME, Krauel K, Marschall T, et al. Complex formation with nucleic acids and aptamers alters the antigenic properties of platelet factor 4. *Blood* 2013; 122(2): 272–281.

21. The Thrombosis and Haemostasis society of Australia and New Zealand. Suspected vaccine induced prothrombotic immune thrombocytopenia (VIPIT): THANZ advisory statement for haematologists, https://www.thanz.org.au/documents/item/577 (2021, accessed 9 April 2021).

22. British Society for Haematology. Guidance produced from the Expert Haematology Panel (EHP) focused on Covid-19 Vaccine induced Thrombosis and Thrombocytopenia (VITT), https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-throm
basis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210407.pdf (2021, accessed 10 April 2021).

23. Neuro Anesthesia & Critical Care Society (NACC). Intensive Care guidance for the management of vaccine-associated thrombocytopenia and thrombosis (VATT), https://www.ics.ac.uk/ICS/Pdfs/Standards_Guidelines/Guidance_for_the_management_of_VATT (2021, accessed 10 April 2021).

24. Avsenik J, Oblak JP and Popovic KS. Non-contrast computed tomography in the diagnosis of cerebral venous sinus thrombosis. *Radiol Oncol* 2016; 50(3): 263–268.

25. Smith CW, Kardeby C, Di Y, et al. Platelet activation by Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) patient serum is blocked by COX, P2Y and kinase inhibitors. *medRxiv*. 2021. DOI: 2021.2004.2024.21255655.

26. Platton S, Bartlett A, MacCallum P, et al. Evaluation of laboratory assays for anti-platelet factor 4 antibodies after ChAdOx1 nCOV-19 vaccination. *J Thromb Haemost*. Epub ahead of print 10 May 2021. DOI: 10.1111/jth.15362.

27. Handtke S, Wolff M, Zaninetti C, et al. A Flow cytometric assay to detect platelet activating antibodies in VITT after ChAdOx1 nCov-19 vaccination. *Blood*. Epub ahead of print 4 May 2021. DOI: 10.1182/blood.2021012064.

**Author biography**

Walid Alam received his bachelor’s degree (BS) in Medical Laboratory Sciences from the University of Balamand’s Faculty of Health Sciences in 2015, and his medical degree (MD) from the University of Balamand’s Faculty of Medicine in 2019. He worked as a house physician in the Emergency Department at the American University of Beirut Medical Center. He has also spent over a year as a postdoctoral research fellow in the Department of Internal Medicine, in the Divisions of Oncology and Infectious Diseases, where he worked on several projects. Dr Alam has also recently joined the American University of Beirut’s Global Health Institute (GHI), an institute that aims to address global health challenges affecting the Middle East and North Africa (MENA) region. He is serving as a Subject Matter Expert to develop an Infectious Diseases Certificate Program for members of the Syrian refugee communities and host communities in Lebanon who are interested in becoming Community Health Workers.