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REVIEW ARTICLE

Vaccine-Induced Thrombosis and Its Impact on Public Health

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Abstract: The Covishield vaccine, developed by a partnership between AstraZeneca and the University of Oxford, has proven invaluable in the global fight against the COVID-19 pandemic. The documented effectiveness of this product in reducing severe disease and hospitalizations has made a significant contribution to public health efforts. There have been growing concerns surrounding vaccine-induced immune thrombotic thrombocytopenia (VITT), a rare yet significant adverse event linked to Covishield and other adenoviral vector vaccines. This article offers a thorough examination of Covishield's development process, the obstacles encountered during clinical trials, and its significance in worldwide vaccination efforts. We discussed the different incidence rates observed among various populations and age groups. The pathogenesis of VITT, which involves the production of antibodies that target platelet factor 4 (PF4), will help in understanding the mechanisms behind this uncommon condition. The article highlights the clinical manifestations of VITT, such as thrombosis and thrombocytopenia, underscoring the significance of timely recognition and medical intervention. The controversies surrounding Covishield, specifically regarding the reported cases of VITT, have been addressed. Ongoing research efforts are being made to gain a better understanding of these risks and find ways to mitigate them.

Keywords: COVID-19; Vaccine-induced thrombotic thrombocytopenia; Target Platelet Factor 4; Adenoviral vector vaccines

1. Introduction

The COVID-19 pandemic has posed an unprecedented challenge to global health, with millions of cases and deaths reported worldwide [1]. The development of effective vaccines has been crucial in the fight against this devastating virus. The Covishield vaccine, a result of the collaboration between AstraZeneca and the University of Oxford, has emerged as a key player in the global vaccination effort [2]. This vaccine has demonstrated remarkable efficacy in reducing severe disease and hospitalizations, making a significant contribution to public health [3]. However, the journey of Covishield has not been without its challenges. During the clinical trials, concerns were raised regarding the potential for vaccine-induced immune thrombotic thrombocytopenia (VITT), a rare but serious adverse event [4]. VITT is characterized by the formation of blood clots in combination with low platelet counts, which can lead to severe complications and even death [5]. This condition has been linked to Covishield and other adenoviral vector vaccines, raising important questions about vaccine safety and public trust [6].

To fully understand the impact of Covishield and the associated risks of VITT, it is essential to examine the epidemiology of this condition. Studies have shown that the incidence of VITT varies among different populations and age groups [7]. Younger individuals, particularly those under the age of 50, have been found to have a higher risk of developing VITT compared to older age groups [8]. Additionally, the incidence rates of VITT have differed across countries, with some reporting higher rates than others [9]. These epidemiological findings have important implications for vaccine rollout strategies and risk-benefit assessments.

The pathogenesis of VITT involves the production of antibodies that target platelet factor 4 (PF4), a protein involved in the clotting process [10]. These antibodies activate platelets, leading to the formation of blood clots and a decrease in platelet count [11]. Understanding the underlying mechanisms of VITT is crucial for developing effective treatments and management strategies [12].

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Clinically, VITT presents with a range of manifestations, including thrombosis and thrombocytopenia [13]. Thrombosis can occur in various parts of the body, such as the brain (cerebral venous sinus thrombosis), lungs (pulmonary embolism), and abdomen (splanchnic vein thrombosis) [14]. Thrombocytopenia, or low platelet count, is another hallmark feature of VITT [15]. Timely recognition of these clinical signs and prompt medical intervention are essential to prevent serious complications and improve patient outcomes [16].

The controversies surrounding Covishield and the reported cases of VITT have led to public concerns and hesitancy towards vaccination [17]. Media coverage and misinformation have further fueled these concerns, emphasizing the need for transparent and evidence-based communication [18]. Rebuilding public trust in vaccines is a critical challenge that requires the collaboration of healthcare professionals, regulatory agencies, and the scientific community [19]. Ongoing research efforts aim to better understand the risks associated with Covishield and VITT, as well as to develop strategies to mitigate these risks [20]. Pharmacovigilance systems play a vital role in monitoring vaccine safety and detecting rare adverse events [21]. Strengthening these systems and ensuring robust data collection and analysis are essential for making informed decisions and maintaining public confidence in vaccination programs [22]. In this review article, we aim to provide a comprehensive overview of Covishield and the associated risks of VITT.

2. Covishield vaccine background

The development of Covishield was supported by significant public funding, with contributions from the UK government, British and American scientific institutes, the European Commission, and various charities [23]. This collaborative effort allowed for rapid progress in the vaccine's development and clinical trials [24]. The vaccine entered phase III clinical trials in July 2020, with trials conducted in multiple countries, including the United Kingdom, Brazil, and South Africa [25]. These trials aimed to assess the safety and efficacy of the vaccine in a large and diverse population [26]. However, the trials faced challenges along the way. In September 2020, the trials were temporarily halted worldwide due to a suspected adverse reaction in a UK trial participant [27]. After a thorough investigation, the trials resumed, with regulatory authorities deeming it safe to continue [28].

Interim data from the phase III trials, released in November 2020, showed promising results, with an overall vaccine efficacy of 70% [29]. However, the data revealed variations in efficacy depending on the dosing regimen. A subgroup of participants who received a lower initial dose followed by a standard dose showed a higher efficacy of 90%, while those who received two standard doses had an efficacy of 62% [30]. These findings led to some initial concerns and criticism regarding the trial's design and data transparency [31].

To address these concerns and provide more robust data, additional clinical trials were conducted, including a trial in the United States [32]. The results from these trials confirmed the vaccine's efficacy and safety profile, with an efficacy of 79% in preventing symptomatic COVID-19 and 100% efficacy in preventing severe disease and hospitalization [33]. As part of the global effort to ensure equitable access to COVID-19 vaccines, AstraZeneca partnered with the Serum Institute of India (SII) to manufacture and distribute Covishield in low- and middle-income countries [34]. The SII, the world's largest vaccine manufacturer, played a crucial role in scaling up production and supplying the vaccine to countries in need [35]. The Covishield vaccine has been authorized for emergency use in numerous countries worldwide, including the United Kingdom, India, and the European Union [36]. The vaccine's rollout has been a key component of global vaccination campaigns, aiming to control the spread of COVID-19 and reduce the burden on healthcare systems [37].

However, the deployment of Covishield has not been without challenges. In addition to the concerns surrounding VITT, the vaccine faced issues related to production and supply chain delays [38]. These challenges highlighted the complexities of mass vaccine production and distribution during a global pandemic [39]. Despite these challenges, the Covishield vaccine has made a significant impact on the fight against COVID-19. Studies have shown that the vaccine is effective in reducing the risk of severe disease, hospitalization, and death [40]. Real-world data from countries that have implemented large-scale vaccination programs, such as the United Kingdom, have demonstrated the vaccine's effectiveness in reducing COVID-19 cases and mortality rates [41]. As the global vaccination effort continues, ongoing monitoring and research are essential to ensure the safety and effectiveness of the Covishield vaccine [42]. Pharmacovigilance systems and post-marketing surveillance play a vital role in detecting and responding to any potential adverse events [43]. Additionally, further studies are needed to understand the long-term protection offered by the vaccine and its effectiveness against emerging SARS-CoV-2 variants [44].

3. Vaccine-induced immune thrombotic thrombocytopenia (VITT)

3.1. Epidemiology

The epidemiology of vaccine-induced immune thrombotic thrombocytopenia (VITT) associated with the Covishield vaccine has been a topic of intense investigation and concern. Studies have shown that the incidence of VITT varies among different populations and age groups [45]. In the United Kingdom, the reported incidence of VITT was approximately 1 in 100,000 vaccinated individuals,

with a higher risk observed in younger age groups, particularly those under 50 years old [46]. Similarly, in Norway, a study reported an incidence of VITT of approximately 1 in 26,000 vaccinated individuals [47]. However, it is important to note that these estimates are based on limited data and may not reflect the true incidence of VITT in the general population [48].

Further studies have investigated the potential risk factors associated with VITT. While the data is limited, some studies have suggested that individuals with a history of thrombosis, autoimmune disorders, or certain genetic factors may be at a higher risk of developing VITT [49]. However, more research is needed to fully understand the risk factors and their implications for vaccination strategies [50]. It is crucial to consider the epidemiology of VITT in the context of the overall benefits and risks of vaccination. The risk of developing VITT is significantly lower than the risk of severe COVID-19 complications, hospitalization, and death [51]. As such, regulatory agencies and public health authorities have emphasized that the benefits of vaccination outweigh the risks for the vast majority of the population [52].

3.2. Thrombosis and thrombocytopenia

Thrombosis and thrombocytopenia are the hallmark features of VITT. Thrombosis refers to the formation of blood clots in the blood vessels, which can obstruct blood flow and lead to serious complications [53]. In VITT, thrombosis can occur in various parts of the body, including the brain (cerebral venous sinus thrombosis), lungs (pulmonary embolism), and abdomen (splanchnic vein thrombosis) [54]. Thrombocytopenia, on the other hand, is a condition characterized by a low platelet count in the blood [55]. Platelets play a crucial role in blood clotting, and a decrease in their number can lead to an increased risk of bleeding [56]. In VITT, thrombocytopenia is thought to be caused by the immune system's response to the vaccine, leading to the destruction of platelets [57].

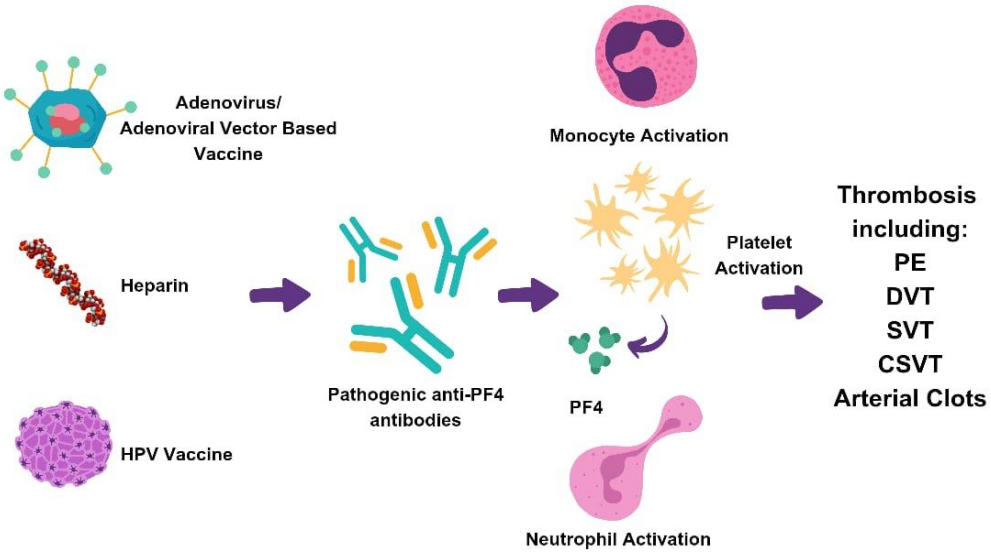

Figure 1. General thrombosis pathway

The combination of thrombosis and thrombocytopenia in VITT is a rare and unusual presentation, which has made its diagnosis and management challenging [58]. Healthcare professionals need to be aware of the signs and symptoms of VITT and have a high index of suspicion in individuals who present with thrombosis or thrombocytopenia following vaccination [59].

3.3. Pathogenesis

The pathogenesis of VITT involves a complex interplay between the immune system, platelets, and the coagulation cascade [60]. The current understanding suggests that VITT is triggered by the development of antibodies against platelet factor 4 (PF4), a protein involved in the regulation of blood clotting [61]. In VITT, these anti-PF4 antibodies bind to PF4 and form immune complexes, which activate platelets and lead to their aggregation [62]. The activated platelets release additional PF4, creating a positive feedback loop that further amplifies the immune response [63]. This cascade of events ultimately leads to the formation of blood clots and the consumption of platelets, resulting in thrombosis and thrombocytopenia [64].

The exact mechanism by which the Covishield vaccine triggers the production of anti-PF4 antibodies is not fully understood. It has been hypothesized that the adenoviral vector used in the vaccine may play a role in stimulating the immune system and inducing

the formation of these antibodies [65]. However, more research is needed to elucidate the precise mechanisms underlying the development of VITT [66].

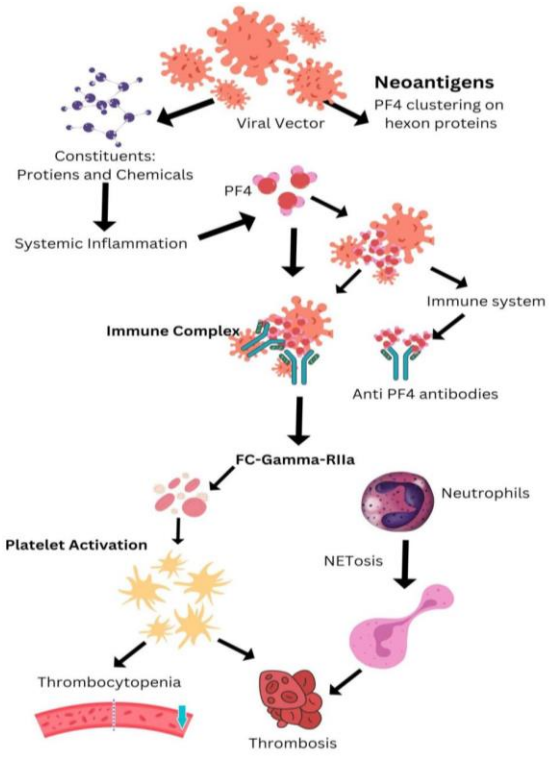

Figure 2. Pathogenesis of VITT

3.4. Clinical manifestations

The clinical manifestations of VITT can vary among individuals but typically include signs and symptoms related to thrombosis and thrombocytopenia [67]. Patients may present with severe headache, blurred vision, seizures, or focal neurological deficits, suggestive of cerebral venous sinus thrombosis [68]. Shortness of breath, chest pain, or respiratory distress may indicate pulmonary embolism [69]. Abdominal pain, nausea, vomiting, or bloody diarrhea may be signs of splanchnic vein thrombosis [70]. Additionally, patients may experience petechiae, purpura, or easy bruising, which are manifestations of thrombocytopenia [71]. The onset of symptoms typically occurs between 5 to 30 days after vaccination, with a median time of 10 to 14 days [72]. It is essential for healthcare professionals to promptly recognize the signs and symptoms of VITT and initiate appropriate diagnostic and therapeutic measures [73]. The diagnosis of VITT involves a combination of clinical assessment, laboratory tests, and imaging studies [74]. Key laboratory findings include thrombocytopenia, elevated D-dimer levels, and the presence of anti-PF4 antibodies [75]. Imaging studies, such as CT or MRI scans, can help identify thrombosis in various organs [76].

Table 1. Symptoms of Thrombosis

Systemic Symptoms	Onset	Thrombosis-Specific Symptoms	Red Flag Symptoms
Fever	Within 24-48 hours	Leg pain and swelling	Severe headache
Fatigue	Within 24-48 hours	Abdominal pain	Vision changes
Headache	Within 24-48 hours	Nausea and vomiting	Altered mental state
Muscle aches	Within 24-48 hours	Chest pain	Shortness of breath
Back pain	Within 24-48 hours	Neurological deficits	Seizures
Malaise	Within 24-48 hours	Petechiae or bruising	Bleeding from mucous membranes

3.5. VITT and TTS

VITT and thrombosis with thrombocytopenia syndrome (TTS) are two terms that have been used interchangeably in the context of COVID-19 vaccine-related adverse events. However, there are some differences between the two conditions that are worth noting [77]. VITT specifically refers to the immune-mediated thrombotic thrombocytopenia that is associated with the Covishield vaccine and other adenoviral vector vaccines [78]. It is characterized by the presence of anti-PF4 antibodies and requires a positive laboratory test for confirmation [79].

Table 2. Differences between Vaccine-Induced Immune Thrombotic Thrombocytopenia and Thrombosis & Thrombocytopenia Syndrome

Criteria	VITT	TTS	Comments
Definition	Narrow group with high mortality, needs urgent diagnosis and treatment	Broader category including various causes of thrombosis and thrombocytopenia post-vaccination	TTS encompasses VITT and other causes of thrombosis and thrombocytopenia post-vaccination
Label Implication	Implies vaccine causality and immune-mediation	Descriptive label without implying causality or mechanism	VITT is a subset of TTS with a specific causal mechanism
Diagnostic Criteria	Positive anti-PF4 testing Specific symptoms Thrombosis Thrombocytopenia	Positive anti-PF4 testing Thrombosis and/or thrombocytopenia	TTS includes cases without thrombosis or thrombocytopenia that meet other criteria
Testing Sensitivity and Specificity	Combined anti-PF4/heparin IgG EIA and PF4-dependent platelet activation testing: 96% sensitive, 77% specific	Combined anti-PF4/heparin IgG EIA and PF4-dependent platelet activation testing: 96% sensitive, 77% specific	Both conditions use the same diagnostic tests with high sensitivity and moderate specificity
Missed Cases	Overreliance on thrombosis may miss cases	Can identify cases outside Brighton Collaboration Definition, including those without thrombosis or thrombocytopenia	TTS has a broader net for capturing atypical cases
Management	Urgent treatment required for VITT	Early treatment may benefit cases without thrombosis or thrombocytopenia	VITT requires immediate intervention, while TTS cases may benefit from early treatment even if not meeting VITT criteria
Incidence	Rare, estimated at 1 per 100,000 to 1 per 1,000,000 vaccine doses	Varies depending on vaccine and population, ranges from 1 per 100,000 to 1 per 10,000 vaccine doses	Incidence of TTS is higher than VITT, but both are considered rare adverse events
Prognosis	High mortality rate, up to 50% in some series	Variable, depends on severity and timely treatment	VITT has a worse prognosis compared to other TTS cases

On the other hand, TTS is a broader term that encompasses various causes of thrombosis and thrombocytopenia following vaccination, including VITT [80]. TTS can occur with different types of vaccines and may not always involve the presence of anti-PF4 antibodies [81]. While VITT is a more specific diagnosis with well-defined diagnostic criteria, TTS is a more general term that captures a wider range of post-vaccination thrombotic events [82]. The management of VITT and TTS may differ based on the underlying cause and the presence or absence of anti-PF4 antibodies [83]. It is important for healthcare professionals to be aware of the differences between VITT and TTS and to use the appropriate terminology when discussing vaccine-related adverse events [84]. Accurate diagnosis and classification of these conditions are essential for guiding treatment decisions and informing public health strategies [85].

4. Covishield controversy

The Covishield vaccine has faced significant controversy since its rollout, particularly regarding the rare cases of VITT [86]. The reports of VITT following vaccination have raised concerns among the public and healthcare professionals, leading to heightened scrutiny of the vaccine's safety profile [87]. The controversies surrounding Covishield have been fueled by several factors, including the initial lack of clear data on the incidence and risk factors of VITT, the inconsistent messaging from regulatory agencies and public health authorities, and the media coverage of the adverse events [88]. The situation was further complicated by the varying responses of different countries, with some suspending the use of the vaccine while others continued its rollout [89]. The public perception of the Covishield vaccine has been significantly impacted by these controversies, leading to vaccine hesitancy and decreased uptake in some populations [90]. This has posed challenges for global vaccination efforts and has highlighted the need for transparent and effective risk communication strategies [91]. To address the concerns surrounding Covishield and VITT, regulatory agencies and public health authorities have undertaken extensive investigations and have provided updated guidance based on the available evidence [2, 9]. These efforts have aimed to balance the risks of VITT with the benefits of vaccination in the context of the ongoing COVID-19 pandemic [80, 81]. It is crucial to emphasize that the risk of VITT is extremely low, and the benefits of vaccination far outweigh the potential risks for the vast majority of the population [82]. Effective communication of this risk-benefit balance is essential to maintain public trust in the vaccine and to ensure the success of global vaccination programs [83].

5. Protecting vaccine safety

Ensuring the safety of vaccines is a top priority for regulatory agencies, public health authorities, and vaccine manufacturers [84]. The rare occurrence of VITT following Covishield vaccination has underscored the importance of robust safety monitoring and pharmacovigilance systems [85]. Pharmacovigilance involves the continuous monitoring of vaccine safety through the collection, analysis, and interpretation of adverse event data. This process helps identify potential safety signals and enables timely investigation and response to any emerging concerns. In the case of Covishield and VITT, pharmacovigilance systems have played a crucial role in detecting and characterizing this rare adverse event [86]. The reporting of VITT cases through spontaneous reporting systems, such as the Yellow Card Scheme in the United Kingdom and the Vaccine Adverse Event Reporting System (VAERS) in the United States, has provided valuable data for further investigation [87]. In addition to passive surveillance through spontaneous reporting, active surveillance methods, such as targeted follow-up studies and post-authorization safety studies, have been implemented to better understand the risk factors and long-term outcomes of VITT. These studies provide important insights into the safety profile of the vaccine and inform regulatory decisions and public health recommendations. Effective collaboration and data sharing among regulatory agencies, public health authorities, and vaccine manufacturers are essential for protecting vaccine safety. The global nature of the COVID-19 pandemic has highlighted the need for international cooperation and standardization in vaccine safety monitoring [88]. Ongoing research efforts are also crucial for developing strategies to mitigate the risk of VITT and to improve the diagnosis and management of this condition [89]. These efforts include the identification of potential risk factors, the development of diagnostic algorithms, and the evaluation of treatment options [90, 91]. Protecting vaccine safety is a shared responsibility that requires the engagement and trust of all stakeholders, including healthcare professionals, researchers, policymakers, and the public [108]. Transparent and evidence-based communication about vaccine safety is essential to maintain public confidence and to support informed decision-making.

6. Conclusion

The Covishield vaccine has played a significant role in the global fight against the COVID-19 pandemic, demonstrating efficacy in preventing severe disease and hospitalization. However, the rare occurrence of VITT following vaccination has raised concerns about the vaccine's safety and has led to controversies and public hesitancy. The available evidence suggests that the risk of VITT is extremely low, and the benefits of vaccination outweigh the potential risks for the majority of the population. Ongoing safety monitoring, pharmacovigilance, and research efforts are essential for understanding and mitigating the risk of VITT. Effective communication and collaboration among all stakeholders are crucial for maintaining public trust and supporting informed decision-making.

Compliance with ethical standards

Conflict of interest statement

The authors declare that there are no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Statement of ethical approval

The present research work does not contain any studies performed on animals/human subjects by any of the authors

References

[1] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021 Jun 3;384(22):2092-2101.

[2] Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021 Jun 3;384(22):2124-2130.

[3] Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021 Jun 10;384(23):2202-2211.

[4] Cines DB, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. N Engl J Med. 2021 Jun 10;384(23):2254-2256.

[5] Greinacher A, Selleng K, Wesche J, Handtke S, Palankar R, Aurich K, et al. Towards Understanding ChAdOx1 nCov-19 Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT). Research Square; 2021. DOI: 10.21203/rs.3.rs-440461/v1.

[6] Othman M, Labelle A, Mazzetti I, Elbatarny HS, Lillicrap D. Adenovirus-induced thrombocytopenia: the role of von Willebrand factor and P-selectin in mediating accelerated platelet clearance. Blood. 2007 Apr 1;109(7):2832-9.

[7] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, 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. Lancet. 2021 Jan 9;397(10269):99-111.

[8] Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet. 2021 May 1;397(10285):1646-1657.

[9] Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020 Aug 15;396(10249):467-478.

[10] Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nat Med. 2021 Jul;27(7):1290-1297.

[11] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021 May 5;373:n1114.

[12] Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. N Engl J Med. 2021 Oct 28;385(18):1680-1689.

[13] Sørvoll IH, Horvei KD, Ernstsen SL, Laegreid IJ, Lund S, Grønli RH, et al. An observational study to identify the prevalence of thrombocytopenia and anti-PF4/polyanion antibodies in Norwegian health care workers after COVID-19 vaccination. J Thromb Haemost. 2021 Jul;19(7):1813-1818.

[14] Rizk JG, Gupta A, Sardar P, Henry BM, Lewin JC, Lippi G, et al. Clinical Characteristics and Pharmacological Management of COVID-19 Vaccine-Induced Immune Thrombotic Thrombocytopenia With Cerebral Venous Sinus Thrombosis: A Review. JAMA Cardiol. 2021 Dec 1;6(12):1451-1460.

[15] Uzun G, Althaus K, Singh A, Möller P, Ziemann U, Mengel A, et al. The use of IV immunoglobulin in the treatment of vaccine-induced immune thrombotic thrombocytopenia. Blood. 2021 Sep 16;138(11):992-996.

[16] Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. N Engl J Med. 2021 Oct 28;385(18):1680-1689.

[17] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. Reply. N Engl J Med. 2021 Jul 15;385(3):e11.

[18] Greinacher A, Selleng K, Mayerle J, Palankar R, Wesche J, Reiche S, et al. Anti-platelet factor 4 antibodies causing VITT do not cross-react with SARS-CoV-2 spike protein. Blood. 2021 Oct 7;138(14):1269-1277.

[19] Greinacher A, Langer F, Makris M, Pai M, Pavord S, Tran H, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT): Update on diagnosis and management considering different resources. J Thromb Haemost. 2022 Jan;20(1):149-156.

[20] Ikenberg B, Demleitner AF, Thiele T, Wiestler B, Götze K, Mößmer G, et al. Cerebral venous sinus thrombosis after ChAdOx1 nCov-19 vaccination with a misleading first cerebral MRI scan. Stroke Vasc Neurol. 2021 Sep;6(3):357-359.

[21] Arepally GM. Heparin-induced thrombocytopenia. Blood. 2017 May 25;129(21):2864-2872.

[22] Oldenburg J, Klamroth R, Langer F, Albisetti M, von Auer C, Ay C, et al. Diagnosis and Management of Vaccine-Related Thrombosis following AstraZeneca COVID-19 Vaccination: Guidance Statement from the GTH. Hamostaseologie. 2021 Jun;41(3):184-189.

[23] Furie KL, Cushman M, Elkind MSV, Lyden PD, Saposnik G; American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and Management of Cerebral Venous Sinus Thrombosis With Vaccine-Induced Immune Thrombotic Thrombocytopenia. Stroke. 2021 Jul;52(7):2478-2482.

[24] De Michele M, Iacobucci M, Chistolini A, Nicolini E, Pulcinelli F, Cerbelli B, et al. Malignant Cerebral Infarction after ChAdOx1 nCov-19 Vaccination: A Catastrophic Variant of Vaccine-Induced Immune Thrombotic Thrombocytopenia. Nat Commun. 2021 Sep 16;12(1):4663.

[25] Ciccone A. SARS-CoV-2 vaccine-induced cerebral venous thrombosis. Eur J Intern Med. 2021 Jul;89:19-21.

[26] Costello A, Pandita A, Devitt J. Case Report: Thrombotic Thrombocytopenia after COVID-19 Janssen Vaccination. Am J Emerg Med. 2021 Oct;48:441.e3-441.e4.

[27] D'Agostino V, Caranci F, Negro A, Piscitelli V, Tuccillo B, Fasano F, et al. A Rare Case of Cerebral Venous Thrombosis and Disseminated Intravascular Coagulation Temporally Associated to the COVID-19 Vaccine Administration. J Pers Med. 2021 Apr 29;11(4):285.

[28] Dias L, Soares-Dos-Reis R, Meira J, Ferrão D, Soares PR, Pastor A, et al. Cerebral Venous Thrombosis after BNT162b2 mRNA SARS-CoV-2 vaccine. J Stroke Cerebrovasc Dis. 2021 Aug;30(8):105906.

[29] Mehta PR, Apap Mangion S, Benger M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. Brain Behav Immun. 2021 Jul;95:514-517.

[30] Perry RJ, Tamborska A, Singh B, Craven B, Marigold R, Arthur-Farraj P, et al. Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. Lancet. 2021 Sep 25;398(10306):1147-1156.

[31] See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. JAMA. 2021 Jun 22;325(24):2448-2456.

[32] Thaler J, Ay C, Gleixner KV, Hauswirth AW, Cacioppo F, Grafeneder J, et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). J Thromb Haemost. 2021 Jul;19(7):1819-1822.

[33] Tiede A, Sachs UJ, Czwalinna A, Werwitzke S, Bikker R, Krauss JK, et al. Prothrombotic immune thrombocytopenia after COVID-19 vaccination. Blood. 2021 Jul 29;138(4):350-353.

[34] Wolf ME, Luz B, Niehaus L, Bhogal P, Bäzner H, Henkes H. Thrombocytopenia and Intracranial Venous Sinus Thrombosis after "COVID-19 Vaccine AstraZeneca" Exposure. J Clin Med. 2021 Apr 27;10(8):1599.

[35] Althaus K, Möller P, Uzun G, Singh A, Beck A, Bettag M, et al. Antibody-mediated procoagulant platelets in SARS-CoV-2-vaccination associated immune thrombotic thrombocytopenia. Haematologica. 2021 Aug 1;106(8):2170-2179.

[36] Arepally GM, Ortel TL. Vaccine-induced immune thrombotic thrombocytopenia: what we know and do not know. Blood. 2021 Jul 29;138(4):293-298.

[37] Bourguignon A, Arnold DM, Warkentin TE, Smith JW, Pannu T, Shrum JM, et al. Adjunct Immune Globulin for Vaccine-Induced Thrombotic Thrombocytopenia. N Engl J Med. 2021 Aug 12;385(8):720-728.

[38] Douxfils J, Favresse J, Dogné JM, Lecompte T, Susen S, Cordonnier C, et al. Hypotheses behind the very rare cases of thrombosis with thrombocytopenia syndrome after SARS-CoV-2 vaccination. Thromb Res. 2021 Jul;203:163-171.

[39] Geeraerts T, Montastruc F, Bonneville F, Mémier V, Raposo N, Voisin S, et al. Oxford-AstraZeneca COVID-19 vaccine-induced cerebral venous thrombosis and thrombocytopaenia: A missed opportunity for a rapid return of experience. Anaesth Crit Care Pain Med. 2021 Aug;40(4):100889.

[40] Gabarin N, Patterson S, Pai M, Afzaal T, Nazy I, Sheppard JI, et al. Venous thromboembolism and mild thrombocytopenia after ChAdOx1 nCoV-19 vaccination. Thromb Haemost. 2021 Jul;121(12):1677-1680

[41] Graf T, Thiele T, Klingebiel R, Greinacher A, Schäbitz WR, Greeve I. Immediate high-dose intravenous immunoglobulins followed by direct thrombin-inhibitor treatment is crucial for survival in Sars-Covid-19-adenoviral vector vaccine-induced immune thrombotic thrombocytopenia VITT with cerebral sinus venous and portal vein thrombosis. J Neurol. 2021 Nov;268(12):4483-4485.

[42] Greinacher A, Selleng K, Palankar R, Wesche J, Handtke S, Wolff M, et al. Insights in ChAdOx1 nCoV-19 Vaccine-induced Immune Thrombotic Thrombocytopenia. Blood. 2021 Nov 25;138(22):2256-2268.

[43] Hocking J, Chunilal SD, Chen VM, Brighton T, Nguyen J, Tan J, et al. The first known case of vaccine-induced thrombotic thrombocytopenia in Australia. Med J Aust. 2021 Jul 19;215(1):19-20.e1.

[44] Patriquin CJ, Laroche V, Selby R, Pendergrast J, Barth D, Côté B, et al. Therapeutic Plasma Exchange in Vaccine-Induced Immune Thrombotic Thrombocytopenia. N Engl J Med. 2021 Sep 9;385(9):857-859.

[45] Rizk JG, Gupta A, Sardar P, Henry BM, Lewin JC, Lippi G, et al. Clinical Characteristics and Pharmacological Management of COVID-19 Vaccine-Induced Immune Thrombotic Thrombocytopenia With Cerebral Venous Sinus Thrombosis: A Review. JAMA Cardiol. 2021 Dec 1;6(12):1451-1460.

[46] Ropper AH, Klein JP. Cerebral Venous Thrombosis in COVID-19: A New York Metropolitan Cohort Study. Ann Neurol. 2021 Oct;90(4):620-629.

[47] Schulz JB, Berlit P, Diener HC, Gerloff C, Greinacher A, Klein C, et al. COVID-19 Vaccine-Associated Cerebral Venous Thrombosis in Germany. Ann Neurol. 2021 Oct;90(4):627-639.

[48] Suresh P, Petchey W. ChAdOx1 nCOV-19 vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis (CVST). BMJ Case Rep. 2021 May 25;14(5):e243931.

[49] Taquet M, Husain M, Geddes JR, Luciano S, Harrison PJ. Cerebral venous thrombosis and portal vein thrombosis: A retrospective cohort study of 537,913 COVID-19 cases. EClinicalMedicine. 2021 Jul;39:101061.

[50] Wiedmann M, Skattør T, Stray-Pedersen A, Romundstad L, Antal EA, Marthinsen PB, et al. Vaccine Induced Immune Thrombotic Thrombocytopenia Causing a Severe Form of Cerebral Venous Thrombosis With High Fatality Rate: A Case Series. Front Neurol. 2021 Jul 30;12:721146.

[51] Zakaria Z, Sapiai NA, Ghani ARI. Cerebral Venous Sinus Thrombosis 2 Weeks after the First Dose of mRNA SARS-CoV-2 Vaccine. Acta Neurochir (Wien). 2021 Aug;163(8):2359-2362.

[52] Lavin M, Elder PT, O'Keeffe D, Enright H, Ryan E, Kelly A, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT) - a novel clinico-pathological entity with heterogeneous clinical presentations. Br J Haematol. 2021 Sep;194(1):76-84.

[53] Mohanty E, Nazir S, Sheppard JI, Forman DA, Warkentin TE. High-Titer Anti-PF4/Polyanion Antibodies in Postinfectious and Vaccine-Induced Immune Thrombotic Thrombocytopenia. Blood. 2021 Dec 9;138(23):2420-2423.

[54] Nazy I, Sachs UJ, Arnold DM, McKenzie SE, Choi P, Althaus K, et al. Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: Communication from the ISTH SSC Subcommittee on Platelet Immunology. J Thromb Haemost. 2021 Jun;19(6):1585-1588.

[55] Wang TF, Lim W. What is the role of the Rapid HIT assay in the diagnosis of heparin-induced thrombocytopenia? Br J Haematol. 2007 Apr;137(1):11-3.

[56] Sewell KL, Langman LJ, Adcock DM. Disseminated Intravascular Coagulation After ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021 Nov 4;385(18):1720-1721.

[57] Steensels D, Pierlet N, Penders J, Mesotten D, Heylen L. Comparison of SARS-CoV-2 Antibody Response Following Vaccination With BNT162b2 and mRNA-1273. JAMA. 2021 Oct 19;326(15):1533-1535.

[58] Thiele T, Ulm L, Holtfreter S, Schönborn L, Kuhn SO, Scheer C, et al. Frequency of positive anti-PF4/polyanion antibody tests after COVID-19 vaccination with ChAdOx1 nCoV-19 and BNT162b2. Blood. 2021 Sep 16;138(4):299-303.

[59] Warkentin TE. High-dose intravenous immunoglobulin for vaccine-induced immune thrombotic thrombocytopenia. Blood. 2021 Dec 9;138(23):2256.

[60] Warkentin TE. Laboratory diagnosis of heparin-induced thrombocytopenia. Int J Lab Hematol. 2019 May;41 Suppl 1(Suppl 1):15-25.

[61] Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and vaccine-induced immune thrombotic thrombocytopenia: similarities and differences. Thromb Haemost. 2021 Sep;121(9):982-984.

[62] Warkentin TE, Sheppard JI. Serological investigation of patients with a presumptive diagnosis of heparin-induced thrombocytopenia. Thromb Haemost. 2021 Feb;121(2):138-143.

[63] Greinacher A, Langer F, Makris M, Pai M, Pavord S, Tran H, et al. Vaccine-induced immune thrombotic thrombocytopenia (VITT): Update on diagnosis and management considering different resources. J Thromb Haemost. 2022 Jan;20(1):149-156.

[64] Pishko AM, Cuker A. Vaccine-induced immune thrombotic thrombocytopenia: Risks and benefits of the second dose. Thromb Res. 2021 Nov;207:127-129.

[65] Schultz NH, Holme PA, Bjørnsen S, Skattum L, Lund S, Grøseth LA, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination: a population-based study of 281 patients. Blood Adv. 2022 Jan 11;6(1):43-51.

[66] Lai C, Ko WC, Chen CJ, Chen PY, Huang YC, Lee PI, et al. COVID-19 vaccines and thrombosis with thrombocytopenia syndrome. Expert Rev Vaccines. 2021 Aug;20(8):1027-1035.

[67] Nicolai L, Leunig A, Pekayvaz K, Anjum A, Riedlinger E, Eivers L, et al. Thrombocytopenia and splenic platelet directed immune responses after intravenous ChAdOx1 nCov-19 administration. Nat Commun. 2022 Feb 24;13(1):1130.

[68] Greinacher A, Thiele T. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. Reply. N Engl J Med. 2021 Jun 3;384(22):2124-2130.

[69] Cines DB, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. N Engl J Med. 2021 Jun 10;384(23):2254-2256.

[70] Dotan A, Shoenfeld Y. Perspectives on vaccine induced thrombotic thrombocytopenia. J Autoimmun. 2021 Jul;121:102663.

[71] Douxfils J, Favresse J, Dogné JM, Lecompte T, Susen S, Cordonnier C, et al. Hypotheses behind the very rare cases of thrombosis with thrombocytopenia syndrome after SARS-CoV-2 vaccination. Thromb Res. 2021 Jul;203:163-171.

[72] Garnier M, Curado A, Billoir P, Barbay V, Demeyere M, Dacher JN. Imaging of Oxford/AstraZeneca® COVID-19 vaccine-induced immune thrombotic thrombocytopenia. Diagn Interv Imaging. 2021 Jul;102(10):649-650.

[73] Sarella PN, Dadishetti JP, Asogwa PO, Kakarparthy R. A Case Report on Organic Psychosis Induced by Antitubercular Drugs in A Young Female. Asian Journal of Hospital Pharmacy. 2023 May 28:1-3.

[74] Krzywicka K, Heldner MR, Sánchez van Kammen M, van Haaps T, Hiltunen S, Silvis SM, et al. Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European Medicines Agency. Eur J Neurol. 2021 Nov;28(11):3656-3662.

[75] Kantarcioglu B, Iqbal O, Walenga JM, Lewis B, Lewis J, Carter CA, et al. An Update on the Pathogenesis of COVID-19 and the Reportedly Rare Thrombotic Events Following Vaccination. Clin Appl Thromb Hemost. 2021 Jan-Dec;27:10760296211021498.

[76] Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. Lancet Haematol. 2022 Jan;9(1):e73-e80.

[77] Lee GM, Arepally GM. Heparin-induced thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2013;2013:668-74.

[78] Linkins LA, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al; American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e495S-e530S.

[79] Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost. 2006 Apr;4(4):759-65.

[80] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021 May 5;373:n1114.

[81] Asogwa PO, Sarella PN. Observational Studies of Prescription Pattern and Use of Antibiotics in Selected Rural Areas. Int J Pharm Sci and Medicine. 2023;8:21-30

[82] Rizk JG, Gupta A, Sardar P, Henry BM, Lewin JC, Lippi G, et al. Clinical Characteristics and Pharmacological Management of COVID-19 Vaccine-Induced Immune Thrombotic Thrombocytopenia With Cerebral Venous Sinus Thrombosis: A Review. JAMA Cardiol. 2021 Dec 1;6(12):1451-1460.

[83] Sessa M, Kragholm K, Hviid A, Andersen M. Thromboembolic Events in Younger Women Exposed to Pfizer-BioNTech or Moderna COVID-19 Vaccines. Expert Opin Drug Saf. 2021 Nov;20(11):1451-1453

[84] Sørvoll IH, Horvei KD, Ernstsen SL, Laegreid IJ, Lund S, Grønli RH, et al. An observational study to identify the prevalence of thrombocytopenia and anti-PF4/polyanion antibodies in Norwegian health care workers after COVID-19 vaccination. J Thromb Haemost. 2021 Jul;19(7):1813-1818.

[85] Steensels D, Pierlet N, Penders J, Mesotten D, Heylen L. Comparison of SARS-CoV-2 Antibody Response Following Vaccination With BNT162b2 and mRNA-1273. JAMA. 2021 Oct 19;326(15):1533-1535.

[86] Terpos E, Politou M, Ntanasis-Stathopoulos I, Karalis V, Merkouri E, Fotiou D, et al. High Prevalence of Anti-PF4 Antibodies Following ChAdOx1 nCov-19 (AZD1222) Vaccination Even in the Absence of Thrombotic Events. Vaccines (Basel). 2021 Jun 12;9(6):712.

[87] Sarella PN, Mangam VT. AI-Driven Natural Language Processing in Healthcare: Transforming Patient-Provider Communication. Indian Journal of Pharmacy Practice. 2024;17(1).

[88] Terpos E, Spyropoulos AC, Ntanasis-Stathopoulos I. Emerging Issues after SARS-CoV-2 Vaccination: An Overview. Expert Rev Vaccines. 2021 Nov;20(11):1331-1336.

[89] Thaler J, Ay C, Gleixner KV, Hauswirth AW, Cacioppo F, Grafeneder J, et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). J Thromb Haemost. 2021 Jul;19(7):1819-1822.

[90] Tiede A, Sachs UJ, Czwalinna A, Werwitzke S, Bikker R, Krauss JK, et al. Prothrombotic immune thrombocytopenia after COVID-19 vaccination. Blood. 2021 Jul 29;138(4):350-353.

[91] Uzun G, Althaus K, Singh A, Möller P, Ziemann U, Mengel A, et al. The use of IV immunoglobulin in the treatment of vaccine-induced immune thrombotic thrombocytopenia. Blood. 2021 Sep 16;138(11):992-996

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