Clinical and Applied Thrombosis/Hemostasis
Volume 27: 1-14

DOI: 10.1177/10760296211021498
journals.sagepub.com/home/cat

# An Update on the Pathogenesis of COVID-19 and the Reportedly Rare Thrombotic Events Following Vaccination

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**Abstract**

Today the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has become a global health problem. After more than a year with the pandemic, although our knowledge has progressed on COVID-19, there are still many unknowns in virological, pathophysiological and immunological aspects. It is obvious that the most efficient solution to end this pandemic are safe and efficient vaccines. This manuscript summarizes the pathophysiological and thrombotic features of COVID-19 and the safety and efficacy of currently approved COVID-19 vaccines with an aim to clarify the recent concerns of thromboembolic events after COVID-19 vaccination. The influx of newer information is rapid, requiring periodic updates and objective assessment of the data on the pathogenesis of COVID-19 variants and the safety and efficacy of currently available vaccines.

**Keywords**

COVID-19, SARS-CoV-2, safety and efficacy, thrombosis, thrombocytopenia, heparin induced thrombocytopenia

Date received: 28 April 2021; accepted: 12 May 2021.

## Introduction

Today the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has become a global health problem. After its first appearance in late December 2019, several healthcare facilities in China reported patients with pneumonia of unknown etiology.[1,2] Although, most of these patients had mild symptoms, a considerable subset of patients developed a more severe condition, varying from pneumonia and acute respiratory distress syndrome (ARDS) to multi-organ failure (MOF).[3-5] There was a pneumonia outbreak of unidentified cause and when investigated, the etiological identification results showed a novel coronavirus as the causative agent.[6] It had rapidly spread to the entire country within 1 month. China implemented strict preventive measures including complete lockdowns in January 2020. Although China reached an epidemic peak in February 2020, with the help of preventive measures, the daily number of

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new cases decreased. However, the international spread of COVID-19 had been observed by late February 2020.[7,8] Despite comprehensive preventive measures, it has continued to spread over every continent and the World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020.[9]

After more than a year with the pandemic, although our knowledge has made great progress on COVID-19, there are still many unknowns in virological, pathophysiological and immunological aspects. Despite numerous efforts, there is still no efficient curative treatment for COVID-19. As of April 2021, more than 130 million people have been infected and more than 2.8 million people have died from COVID-19.[10] The catastrophe that it created threatened healthcare systems, disrupted the global economy and changed all of our lives. It is obvious that the most efficient solution to end this pandemic is to vaccinate the general population.[11]

The development of the vaccines started as soon as the virus genome was published in early January 2020.[12,13] As of April, 9 2020, there have been 186 vaccine candidates for COVID-19 and 87 of them have started human clinical trials.[14] Many different vaccine technology platforms have been used to develop a safe and effective vaccine. Currently, 4 different vaccine platforms are approved for use. These comprise nucleic acid (mRNA) platforms, viral vector platforms, inactivated virus platforms and subunit vaccine platforms.[15-17] Among these platforms, 11 vaccines showed promising results that allowed them to gain emergency approval for use in different parts of the world. The emergence of new variants of SARS-CoV-2 is another problem in vaccine development. Recently, 3 SARS-CoV-2 variants, B.1.1.7 (501Y.V1), B.1.351 (501Y.V2) and B.1.1.28.1 (P.1), have emerged in the United Kingdom, South Africa and Brazil, respectively.[18]

The latest estimates on COVID-19 suggest that a range of 60%-75% immunization would be necessary to control the spread of SARS-CoV-2.[19-21] COVID-19 vaccine acceptance rates vary from 23.6% to 97% in different countries.[22] Vaccine hesitancy is a growing problem for the success of COVID-19 immunization programs.[23] Survey studies showed that information on vaccine effectiveness and safety or adverse effects are important factors for public acceptance of vaccines.[24,25] The current evidence indicates that there is no proven link between COVID-19 vaccines and thrombotic disorders. However, the appearance of thrombotic events after vaccinations in public media has raised concerns about their safety.

In this manuscript, the pathophysiological, thrombotic features of COVID-19, and the safety and efficacy of currently approved COVID-19 vaccines are summarized with an aim to address and clarify the recent concerns of thromboembolic events after COVID-19 vaccination.

## Pathophysiology of COVID-19 and Associated Thrombosis

SARS-CoV-2, the causative agent of COVID-19, is a single-stranded positive-sense RNA virus that is classified in the genus *Betacoronavirus*.[26] Its genome is composed of non-structural protein (nsp) genes encoded within the 5′ end and structural protein genes in the 3′ end. The non-structural proteins are responsible for vital functions of the virus such as viral replication, transcription, production of RNA processing and modifying enzymes. The structural proteins are spike (S), membrane (M), and envelope (E) proteins that are expressed on the envelope of the virion, and the nucleocapsid (N) protein that forms a helical ribonucleocapsid structure by binding to genomic RNA inside the virion. The S protein is located on the viral surfaces, forming trimeric structures.[26,27]

The first step of coronavirus infection is the binding of the coronavirus spike (S) protein to the cellular entry receptor, angiotensin converting enzyme 2 (ACE2).[28,29] Coronavirus S proteins are fusion glycoproteins that are divided into 2 functionally distinct parts (S1 and S2). S1 is located on the virus surface and contains the receptor-binding domain (RBD) that specifically binds to the host cell receptor. The transmembrane S2 domain contains the fusion peptide, which mediates the fusion of viral and cellular membranes.[30,31] Besides receptor binding, the proteolytic cleavage of coronavirus S proteins by host cell-derived proteases is essential to permit this fusion. SARS-CoV-2 has been shown to use the cell-surface serine protease TMPRSS2 for priming and entry of the virus.[32,33] ACE2 is expressed in various human organs including oral and nasal epithelium, nasopharynx, lung, small intestine, kidney, spleen, liver, colon, brain and also the vascular endothelium.[34] However, its expression in the lungs is relatively lower when it is compared to other organs. In fact, TMPRSS2 is expressed in the human respiratory tract and thus strongly contributes to both SARS-CoV-2 spread and pathogenesis.[35,36] After entry of the SARS-CoV-2 into the host cells, it starts to express and replicate its genomic RNA to produce full-length copies that are incorporated into newly produced viral particles.

Once SARS-CoV-2 enters the target cells, the infection generally manifests itself as asymptomatic or mild upper respiratory tract disease, but it can also manifest as a severe disease such as severe respiratory failure, ARDS and MOF.[37] In this regard, it has been theorized that early-stage infection (Stage I) starts after entry of the virus into the host cell with high viral replication commonly presenting with a wide range of complaints including mild cold-like signs and symptoms. If the infection is not restricted at this stage, it progresses into pulmonary phase (Stage II) which occurs with selective injury of the virus to lung parenchyma. This is generally manifested by shortness of breath, hypoxia and pulmonary infiltrates with some degree of lung inflammation during the COVID-19 disease state. Further progression of the disease causes an exaggerated host immune-inflammatory response to the virus (Stage III), that has recently been termed as "cytokine storm" leading to ARDS and MOF.[38] Here, it is important to acknowledge that the boundaries of these stages are not clear and vary according to the patient. Individuals particularly at risk for severe disease include the elderly, males, and those with pre-existing diseases such as cardiovascular disease, diabetes, obesity, chronic respiratory disease, and immune-suppressed conditions.[39,40]

However, it is impossible to predict the outcome in a certain patient.

Currently, we know that the manifestations and developments of COVID-19 are caused by overlapping and complex interactions of different pathophysiological mechanisms.[41,42] In this regard, one of the proposed mechanisms is down regulation of ACE2 over the course of COVID-19 infection. In a healthy person, angiotensinogen, produced in the liver, is cleaved by renin, resulting in formation of angiotensin I (AT-I). AT-I is converted by ACE to angiotensin II (AT-II). AT-II is the most potent component of Renin-Angiotensin-Aldosterone System (RAAS), and has major effects such as vasoconstriction, renal sodium reabsorption and potassium excretion, aldosterone synthesis, blood pressure elevation and induction of inflammatory and pro-fibrotic pathways. ACE2 cleaves AT-II into AT (1-7), which exerts vasodilating, anti-inflammatory and anti-fibrotic effects through binding to the MAS receptor. In addition, ACE2 cleaves AT-I into AT (1-9), which is in turn converted into AT (1-7). This mechanism is usually of less physiological importance. Therefore, ACE2 functionally counteracts the physiological role of ACE, and the eventual effects of RAAS activation. ACE2 also affects bradykinin metabolism in the lungs by inactivating des-Arg bradykinin, thereby inhibiting effects like vasodilation and elevation of vascular permeability. In fact, down regulation ACE2 during COVID-19 is expected to cause inappropriate activation of RAAS and increased bradykinin effects in the lungs of the patients.[43,44]

It has been shown that the first response mechanism to viral infections is innate immunity.[45] In a healthy person, in case of a viral entry, viral pathogen-associated molecular patterns (PAMPs) are recognized by endosomal pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) or Retinoic acid inducible-I (RIG-I) receptors. Binding with these receptors causes an activation of intracellular signaling pathways, which results with the activation of transcription factors such as nuclear factor-kappa B (NF-κB) and interferon regulatory factors (IRFs). This facilitates the production of type I and III interferons as well as pro inflammatory cytokines. An appropriate IFN response is crucial to limit the viral replication and induction of apoptosis to protect the host from viral dissemination.

In SARS-CoV-2 infection, as a characteristic feature of coronavirus family, replication organelles such as double-membrane vesicles (DMVs), convoluted membranes (CM) and double-membrane spherules (DMS) are produced preventing the exposure of viral replication intermediates to cytosolic innate immune sensors. Additionally, multiple SARS-CoV-2 non-structural proteins (e.g. open reading frame 6 (ORF6) and ORF3b) have also been shown to suppress IFN production and signaling. This causes an initial delay of IFN production in COVID-19, causing unrestricted viral replication and dissemination in the infected host.[46-48] However, initial suppression of immune response eventually causes a rebound increase in IFN production and secretion of large amounts of inflammatory cytokines, resulting in overactivation of the immune system and organ damage. Hypercytokinemia that has been reported in severe COVID-19, is often referred to as a "cytokine storm" or "macrophage activation syndrome" (MAS). However, the degree of pro-inflammatory cytokinemia in COVID-19 has been shown to be profoundly less than classical MAS.[49,50]

An additional consideration in relationship with the innate immune system is the complement system. It acts as a rapid immune surveillance system against invading pathogens, connecting innate and adaptive immunity.[49] It has been observed that there is a high degree of complement activation in COVID-19, resulting with pathologic acute and chronic inflammation, endothelial cell dysfunction, and intravascular coagulation.[51-53]

The adaptive immune system is also an important defense mechanism in COVID-19. While CD8+ T cells destroy the infected cells to control the infection, the neutralizing antibodies produced by B cells provide humoral immunity. An important feature of COVID-19 is absolute lymphopenia, with reduced numbers of CD4+ T-cells, CD8+ T-cells, and B-cells. The reasons for lymphopenia in COVID-19 can be listed as: low IFN levels, direct SARS-CoV-2 infection of T-cells, cytokine-induced apoptosis of lymphocytes, MAS-related hemophagocytosis, sequestration of lymphocytes in the lungs or other organs, reduced bone marrow production and virus-induced tissue damage of lymphatic organs. Nevertheless, most of the COVID-19 patients with mild to moderate disease experience a robust adaptive immune response comprised of T-cells (against S-protein- and nucleoprotein/membrane protein-derived antigens) and neutralizing antibodies (against S-protein-derived antigens), which persists for months after primary infection.[54-61]

Autoimmunity and autoinflammation represent additional aspects of COVID-19 pathophysiology.[62] In this regard, several mechanisms have been postulated for development of autoimmunity. Primarily, the molecular mimicry of some proteomes between human and SARS-CoV-2 peptides is an important finding. Interestingly, this mimicry was not found in mammals unaffected by SARSCoV-2.[63] As the adaptive immune system produces neutralizing antibodies to common molecules among pathogens, this molecular mimicry can possibly result in the development of autoimmunity.

Neutrophil extracellular traps (NETs) activation and release are other players which may drive autoimmunity in the pathophysiology of COVID-19. Normally after NETs have been released by activated neutrophils, they produce frameworks that comprise of neutrophil-derived DNA and acetylated histones, which trap and kill invading pathogens while minimizing damage to the host cells. Neutrophilia, increased neutrophil-associated cytokine responses and excessive NET formation is a common finding in COVID-19.[64-66] It is important to note that NETs can promote activation of both the intrinsic and extrinsic coagulation pathways by activation of factor VII and binding to TF, which is called immune-thrombosis.[67-69]

Additionally, NETs can also serve as a source of self-antigens resulting in autoimmune conditions. It has been postulated that NET-derived neutrophil proteases, such as elastase, may cause the release of peptidylarginine deiminases (PADs)

that enhance citrullination of self-proteins (e.g. histones, cartilage proteins and others), rendering them for autoreactive and autoinflammatory cascades. Excessive NET formation has also been observed in various autoimmune diseases such as SLE, RA, dermatomyositis, antiphospholipid syndrome (APS) and multiple sclerosis (MS).[70-73]

Another potential driver of autoimmunity is the autoantibody that is produced in the course of COVID-19 infections. It is well known that many viruses can trigger autoimmunity. Similarly, numerous reports have shown that COVID-19 patients develop multiple types of autoantibodies. Some of the antibodies that have been reported during the course of COVID-19 can be listed as anticardiolipin (aCL), lupus anticoagulant (LAC), beta2 glycoprotein I (β2GPI), antinuclear antibodies (ANA), p-ANCA, c-ANCA, anti-CCP and anti-heparin-PF4 (aPF4) antibodies.[74-79] Notably, these antibodies are observed mostly in severely ill patients of COVID-19 rather than with mild or moderate disease. This observation suggests that generalized hyperinflammatory polyclonal B cell activation may be another leading cause for development autoimmunity in the course of COVID-19.[80,81]

Apart from these causative factors regarding molecular mimicry such as excessive NET formation or antibody production, during the course of COVID-19, new onset autoimmune disorders have also been observed. In this regard, multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults (MIS-A) have emerged as unique autoimmune disorders during COVID-19.[82-85] However, numerous autoimmune conditions triggered by COVID-19 have also been published, including Guillain-Barré syndrome (GBS), immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA), thrombotic thrombocytopenic purpura (TTP), antiphospholipid syndrome (APS) and heparin-induced thrombocytopenia (HIT).[79,86-89]

In summary, thrombotic complications and coagulopathy frequently occur during COVID-19. The high rates of venous and arterial thromboembolism in usual and unusual sites have been related with high rates of morbidity and mortality. Since there are many unknowns about COVID-19, the thrombotic complications may be the result of different conditions such as DIC, MAS, APS, TTP/HUS and HIT.[90] This complicates the diagnostic processes and causes many difficulties in treatment. Due to these risks, vaccination programs and simple prevention measures (masks, physical distance, hygiene) are the most important in the fight against COVID-19.

## Safety and Efficacy of Currently Approved COVID-19 Vaccines

### *mRNA Vaccines*

BNT162b2 is a lipid nanoparticle (LNP) formulated, nucleoside-modified messenger RNA (mRNA) vaccine, which encodes the receptor binding domain (RBD) of the S1 protein (Table 1). The RBD is constructed on a T4-fibritin derived fold on trimerization base, which helps to guide antigen folding into the native trimeric state. The N-methyl pseudo-uridine (m1Ψ) nucleoside modification protects it from innate immunity. It is encapsulated with an LNP that protects it from enzymatic degradation and ensures efficient cellular uptake.[15-17] In the Phase 1 clinical trial, BNT162b2 elicited high SARS-CoV-2 neutralizing antibody titers with robust T cell responses. In addition, side effects were also acceptable, which were mainly composed of short-term local (i.e., injection site) and systemic responses.[91]

In the Phase 3 clinical trial, a total of 43,448 participants received vaccinations: 21,720 with BNT162b2 and 21,728 with placebo.[92] A 2-dose regimen of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older. Local reactions were common and included pain, erythema and swelling at injection sites. Transient systemic reactions such as fever, fatigue, headache, and muscle and joint pain were also noted. The number of serious adverse events that were reported were similar, showing 126 (0.6%) serious adverse events reported in the vaccine group and 111 (0.5%) serious adverse events in the placebo group. Only 4 serious adverse events (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia) can be related with BNT162b2. During follow-up, 2 BNT162b2 recipients (one from arteriosclerosis, one from cardiac arrest), and 4 placebo recipients (2 from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction) have died. No deaths were considered to be related to the vaccine or placebo.

mRNA-1273 is another mRNA vaccine approved for use. It encodes the prefusion form of the S antigen that includes a transmembrane anchor and an intact S1−S2 cleavage site. Two proline substitutions in the vaccine mRNA keep the protein stable in its prefusion conformation. It is also encapsulated with an LNP.[15-17] In the Phase 1 dose escalation clinical trial, mRNA-1273 showed encouraging results in safety and immunogenicity.[93]

In the Phase 3 trials, 30,420 volunteers were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group).[94] The efficacy has been reported as 94.1% for the prevention of symptomatic SARS-CoV-2 infection and 100% for preventing severe COVID-19 as compared with placebo. Although transient local and systemic reactions were higher in the vaccine recipients, the frequency of unsolicited adverse events, unsolicited severe adverse events, and serious adverse events reported during the study period were generally similar among participants in the 2 groups. Three deaths occurred in the placebo group: (one from intraabdominal perforation, one from cardiopulmonary arrest, and one from severe systemic inflammatory syndrome in a participant with chronic lymphocytic leukemia and diffuse bullous rash) and 2 in the vaccine group (one from cardiopulmonary arrest and one by suicide).

### *Non-Replicative Vector Vaccines*

ChAdOx1-S, currently named as AZD1222, employs a different viral vector, an *Adenovirus* derived from the chimpanzee.

**Table 1.** Currently Approved COVID-19 Vaccines.

| Vaccine | Developer | Vaccine composition | Country of the vaccine producer | Vaccine platform | Number of doses & schedule | Route of administration | Storage conditions | Current status of clinical evaluation | Efficacy | Safety in clinical studies |
|---|---|---|---|---|---|---|---|---|---|---|
| mRNA-BNT162b2-Comirnaty | Pfizer/BioNTech + Fosun Pharma | mRNA vaccine encoding for the RBD of the S1 protein. Vaccine contains single nucleoside incorporations of 1-methylpseudouridine. RBD antigen contains a T4 fibritin-derived fold-on trimerization domain. Encapsulated within an LNP. | USA-Germany | mRNA | 2<br>Day 0 + 21 | IM | Stored at −70 °C<br>Stored at −25 to −15 °C for 2 weeks<br>Stored 2-8 °C for 5 days | Phase 4 | 95% | Phase 3 results showed safety. (Published) |
| mRNA-1273 | Moderna + National Institute of Allergy and Infectious Diseases | mRNA vaccine encoding for the profusion form of the S antigen that includes a transmembrane anchor and an intact S1-S2 cleavage site in its profusion form. Encapsulated within an LNP. | USA | mRNA | 2<br>Day 0 + 28 | IM | Stored at −20 °C<br>Stored 2-8 °C for 30 days | Phase 4 | 94.1% | Phase 3 results showed safety. (Published) |
| ChAdOx1-S-AZD1222 | AstraZeneca + University of Oxford | Adenovirus derived from chimpanzee with E1 and E3 deletions, encoding for the full-length S protein with a tissue plasminogen activator signal peptide. | United Kingdom-Sweden | Non-replicating Viral Vector | 1-2<br>Day 0 + 28 | IM | Stored under refrigeration | Phase 4 | 70.4% | Phase 3 results showed safety. (Published) |
| Sputnik V | Gamaleya Research Institute + Health Ministry of the Russian Federation | Adenovirus based vaccine combining 2 adenoviruses: Ad5 and Ad26. | Russia | Non-replicating Viral Vector | 2<br>Day 0 + 21 | IM | The vaccine was manufactured as 2 formulations, frozen and lyophilized. | Phase 3 | 91.6% | Phase 3 results showed safety. (Published) |
| Ad26.COV2.S-JNJ-78436735 | Johnson & Johnson + Janssen Pharmaceutical | Recombinant, replication incompetent adenovirus serotype 26 (Ad26) vector encoding a full length and stabilized SARS-CoV-2 spike (S) protein. The vaccine was derived from the first clinical isolate of Wuhan strain. | USA-Germany | Non-replicating Viral Vector | 1-2<br>Day 0 + 56 | IM | Stored at −20 °C for 2 years<br>Stored 2-8 °C for 3 months | Phase 3 | 72% | Phase 3 results showed safety. (Published) |
| Convidecia | CanSino Biological Inc. + Beijing Institute of Biotechnology | Ad5 with E1 and E3 deletions encoding for the full-length S protein. Gene was derived from the Wuhan-Hu-1 sequence for SARS-CoV2 and contains a tissue plasminogen activator signal peptide. | China | Inactivated | 1<br>Day 0 | IM | Stored under refrigeration. | Phase 3 | 65.28% | Phase 3 results showed safety. (Unpublished) |
| BBIBP-CorV | Sinopharm + China National Biotec Group Co | β-propionolactone inactivated vaccine of SARS-CoV-2 | China | Inactivated | 2<br>Day 0 + 21 | IM | Stored under refrigeration. | Phase 3 | 79.34% | Phase 3 results showed safety. (Unpublished) |
| CoronaVac | Sinovac Research and Development Co., Ltd | β-propionolactone inactivated vaccine of SARS-CoV-2 | China | Inactivated | 2<br>Day 0 + 14 | IM | Stored under refrigeration. | Phase 4 | 50.38%-83.5% | Phase 3 results showed safety. (Unpublished) |
| BBV152-Covaxin | Bharat Biotech International Limited | BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine formulated with a Toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) or alum (Algel). | India | Inactivated | 2<br>Day 0 + 14 | IM | Stored under refrigeration.<br>Stable in room temperature for 1 week. | Phase 3 | 81% | Phase 3 results showed safety. (Unpublished) |
| NVX-CoV2373 | Novavax | Stable profusion, full-length S protein made from VLP nanoparticle technology, given with saponin-based adjuvant, Matrix-M™. | USA | Subunit | 2<br>Day 0 + 21 | IM | Stored under refrigeration. | Phase 3 | 96.4% | Phase 3 results showed safety. (Unpublished) |
| EpiVacCorona | Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector" | The vaccine contains small portions of viral proteins, known as peptides. | Russia | Subunit | 2<br>Day 0 + 21 | IM | Stored 2-8 °C for 2 years | Phase 3 | 100% | Phase 3 results showed safety. (Unpublished) |

The use of a chimpanzee vector minimizes the possibility of interaction with preformed antibodies against adenoviruses. While the E1 deletion blocks the viral replication, the E3 deletion enables incorporation of larger genetic cargo into the viral vector. The added sequence encodes for the full-length S protein with a tissue plasminogen activator signal sequence. The S protein sequence is codon-optimized.[15-17] In the Phase I clinical trial, the results showed no severe side effects with efficient humoral and cellular immune responses.[95,96] On the basis of these results, they launched their Phase 2-3 trials. In a recent interim analysis of Phase 2-3 trials, the outcomes of 11,636 from 23,848 totally enrolled participants have been published.[97,98] Overall vaccine efficacy has been reported as 70.4%. Interestingly, while the efficacy in participants who received 2 standard doses was 62.1%, the efficacy in participants who received a low dose followed by a standard dose was 90.0%. In a 74,341 person/months of safety follow-up 175 severe adverse events have been observed in 168 participants, 84 events in the AZD1222 group and 91 in the control group. However, only 3 events were initially considered to be vaccine related. These events were: a case of transverse myelitis in vaccine group that the independent neurological committee considered the most likely diagnosis to be idiopathic, a case of hemolytic anemia in the control group, and an individual who recorded fever higher than 40 °C, but who recovered rapidly without an alternative diagnosis and was not admitted to hospital, who remains masked to group allocation. There were 4 non-COVID-19 deaths reported across the studies (3 in the control arm and one in the AZD1222 arm) that were all considered unrelated to the vaccine.

Sputnik V is an adenovirus-based vaccine combining 2 adenoviruses, rAd5 and rAd26 designed by the collaboration of the Gamaleya Research Institute with the Health Ministry of the Russian Federation.[15-17] Both have been developed as frozen and lyophilized formulations. In the Phase 1 clinical trial, the vaccine showed high efficacy with a low side effect profile. The most common side effects were pain at the injection site, hyperthermia, headache, fatigue and muscle/joint pain. These adverse events were mostly mild and no serious adverse events reported.[99] The Phase 3 clinical trial involved 21,977 participants, showing a vaccine efficacy of 91.6%.[100] While most reported adverse events were grade 1, 45 of 16,427 participants in the vaccine group and 23 of 5,435 participants in the placebo group had serious adverse events. None were considered to be associated with vaccination by the independent data monitoring committee. Four deaths were reported during the study period. Three participants (1 death is due to thoracic vertebral fracture, 2 deaths are due to COVID-19 infection) were in the vaccine group, 1 participant (due to hemorrhagic stroke) in the placebo group. None of the deaths are considered to be vaccine related. Russia approved Sputnik V in August 2020.

Ad26.COV2.S is a recombinant non replicating viral vector vaccine that uses adenovirus serotype 26 (Ad26). The vector encodes a full length and stabilized SARS-CoV-2 spike (S) protein. The vaccine gene was derived from the first clinical isolate of Wuhan strain.[15-17] The safety and efficacy have been studied in 805 participants in Phase 1 and 2 clinical trials.[101] In these trials, regardless of vaccine dose or age group, neutralizing antibody titers against wild-type virus were detected in 90% or more of all participants with accompanying T cell responses.

The results of Phase 3 clinical trials have been published recently.[102] In January 2021, Johnson & Johnson announced that the efficacy of their vaccine is 72% in the USA, 64% in South Africa and 61% in Latin America. The local and systemic adverse events were mostly mild or moderate. Severe adverse events have been reported in 83 of vaccine recipients (N = 21,895) and 96 of placebo recipients (N = 21,888). A numerical imbalance for venous thromboembolic events (11 in the vaccine group vs. 3 in the placebo group) were observed. Deep venous thrombosis has been reported in 6 of vaccine and 2 of placebo recipients. Pulmonary embolism has been reported in 4 of vaccine and 1 of placebo recipients. Transverse sinus thrombosis has been reported in 1 of the vaccine and none of the placebo recipients. Seizures have been reported in 4 of vaccine and 1 of placebo recipients. Tinnitus has been reported in 6 of the vaccine and none of the placebo recipients. For these imbalances, no causal relationship can be determined. Three deaths were reported in the vaccine group and 16 in the placebo group, all of which were considered by the investigators to be unrelated to the trial intervention. No deaths related to COVID-19 were reported in the vaccine group, whereas 5 deaths related to COVID-19 were reported in the placebo group. Transverse sinus thrombosis with cerebral hemorrhage and a case of Guillain-Barré syndrome were each seen in 1 vaccine recipient. In the light of these findings, the United States Food and Drug Administration (FDA) issued an emergency use authorization in February 2021.

Convidecia is another non-replicating adenoviral (Ad5) vector vaccine encoding for the full-length S protein. The vaccine gene was derived from the Wuhan-Hu-1 sequence for SARS-CoV2. Similar to the AZD1222 vaccine, the gene of the vaccine contains E1 and E3 deletions with a tissue plasminogen activator signal sequence.[15-17] In the Phase 1 dose-escalation trial, 108 participants have reported high levels of neutralizing antibody titers with specific T cell responses. No serious adverse events have been reported.[103] In the phase 2 trial, 508 participants were included. In this trial Convidecia induced significant immune responses and no serious adverse events reported.[104] The Phase 3 clinical trials have been launched with these results. The results of this trial have not been published yet. CanSino Biologics announced that the vaccine has an efficacy rate of 65.28%. China approved the vaccine for general use in February 2021.

## *Inactivated Vaccines*

BBIBP-CorV is a propionolactone inactivated SARS-CoV-2 vaccine. The inactivated virus was isolated from a patient in the Jinyintan Hospital in Wuhan. (HB02 Strain) The virus was cultivated in a qualified Vero cell line for propagation.[15-17] In the Phase 1 and 2 clinical trials, a robust humoral immune response was observed in 100% of vaccine recipients.[105,106]

All adverse reactions were mild or moderate in severity. No serious adverse events were reported within 28 days post vaccination for all cohorts. The Phase 3 clinical trials have been launched with these results. The results of these trials have not been published yet. Sinopharm CNGB announced that the vaccine has an efficacy rate of 79.34%. China approved the vaccine for general use in December 2020.

Coronavac is a propiolactone inactivated SARS-CoV-2 vaccine. The inactivated virus was isolated from a patient in the Jinyintan Hospital in Wuhan. (CN02 strain) The virus was cultivated in a qualified Vero cell line for propagation.[15-17] In the Phase 1 and 2 clinical trials, the vaccine-induced neutralizing antibodies in 100% of vaccine recipients.[107,108] There were no severe adverse reactions reported in any of the groups. Phase 3 clinical trials started in July 2020. The results of this trial have not been published yet. Sinovac announced that the vaccine has an efficacy rate of 50.65% for all cases (83.70% for cases requiring medical treatment, and 100.00% for hospitalized, severe, and fatal cases). There was no serious adverse event related to vaccination. China approved the vaccine for general use in February 2021.

BBV152-Covaxin is a whole-virion inactivated SARS-CoV-2 vaccine designed by Bharat Biotech International Limited. It has been designed with 2 adjuvant forms, using aluminum (Algel) or an imidazoquinoline molecule, which is a toll-like receptor (TLR) 7/8 agonist absorbed to aluminum (Algel-IMDG).[15-17] In the Phase 1 clinical trial, 375 participants have been enrolled. BBV152-Covaxin elicited efficient SARS-CoV-2 neutralizing antibody titers and T cell responses.[109] Local and systemic side effects were mild or moderate and were more frequent after the first dose. Only 1 serious adverse event (Viral Pneumonitis) has been reported, which was not related to the vaccine. In the Phase 2 clinical trial, 380 participants were enrolled.[110] This study showed that BBV152-Covaxin has elicited high levels of neutralizing antibodies that remained elevated in all participants 3 months after the second vaccination. No serious adverse events were reported in this study. Phase 3 clinical trials started in December 2020 with these results. The results of this trial have not been published yet. The Indian Government granted emergency use authorization in January 2021. Bharat Biotech International Limited announced interim Phase 3 clinical trial results of 25,800 participants that showed that BBV152-Covaxin demonstrated 81% efficacy and severe, serious and medically attended adverse events occurred in low levels and were similar between vaccine and placebo groups.

### *Subunit Vaccines*

NVX-CoV2373 is a recombinant SARS-CoV-2 (rSARS-CoV-2) nanoparticle vaccine constructed from the full-length (including the transmembrane domain) and wild-type SARS-CoV-2 spike glycoprotein. The vaccine was designed with a special adjuvant called Matrix-M ™. Matrix-M ™, an adjuvant based on saponin extracted from the *Quillaja saponaria* Molina tree induces high and long-lasting levels of broadly reacting antibodies supported by a balanced TH1 andTH2 type of response. Although the mode-of-action of Matrix-M adjuvant has not been elucidated in detail; the adjuvant promotes rapid and profound effects on cellular drainage to local lymph nodes creating a milieu of activated cells including T cells, B cells, Natural Killer cells, neutrophils, monocytes and dendritic cells. From the previous vaccine studies, it has shown a significant dose-sparing effect and an acceptable safety profile.[15-17] In the Phase 1-2 clinical trial, 83 participants were enrolled to receive the vaccine or placebo.[111] At 35 days, NVX-CoV2373 elicited immune responses that exceeded levels in COVID-19 convalescent serum. No serious adverse events were reported. After these results, Phase 3 clinical trials have been launched in many different countries around the world. The results of these trials have not been published yet. Novavax announced interim Phase 3 clinical trial results in U.K. and South Africa in March 2021. The results of these studies showed 100% efficacy in preventing severe disease. The overall efficacy was 96.4%. In both the U.K. and South Africa trials, the vaccine was well-tolerated, with low levels of severe, serious and medically attended adverse events at day 35, balanced between vaccine and placebo groups. Novavax announced that their vaccine may get authorization by the US FDA in May 2021.

EpiVacCorona is a subunit vaccine containing chemically synthesized peptide immunogens corresponding to selected protective epitopes of SARS-CoV-2 coronavirus S protein, conjugated to recombinant SARS-CoV-2 protein N, as a carrier, adjuvanted with aluminum hydroxide.[15-17] The Phase 1-2 trials were published in March 2021. In this study, the 2-dose vaccination scheme induced the production of antibodies specific to the antigens that make up the vaccine in 100% of the volunteers.[112] No serious adverse events have been reported. Phase 3 clinical trials were registered in March 2021 and have not been published yet.[113] Russia approved EpiVacCorona in October 2020. Turkmenistan approved EpiVacCorona in January 2021.

## Thrombotic Events After COVID-19 Vaccines

Following the approval of several different vaccines, by late December 2020 mass vaccination campaigns have started all around the world. After 1 year of the COVID-19 pandemic, availability of a vaccine brought much needed relief and hope for everyone in the fight against COVID-19. However, several thrombotic events related to the AZD1222 vaccine reported in early March 2021 raised concerns in the medical community and the public sector. After these reports, the European Medical Association (EMA) started an assessment.[114]

In this assessment covering a population of 5.5 million who have been vaccinated with the AZD1222 vaccine, the results for overall thrombotic events were exceedingly rare. However, a signal of disproportionality was noted for rare events, such as DIC, cerebral venous sinus thrombosis (CVST) and hemorrhagic stroke. This disproportionality was more evident in vaccine recipients under 60 years of age. In the EMA's assessment,

202 serious cases were identified in which 22% (45) were fatal. Most cases (122) were female. There were 7 cases (4 fatal) of DIC and 18 cases (6 fatal) of CVST. 8 additional CVST cases were added during the assessment period. In these cases, a chronological pattern is observed, with a first reaction to the vaccine observed within a few days after the vaccination. This episode usually lasts 2 or 3 days and is followed, often after a healthy interval, by a period of deterioration from 6 to 12 days after vaccination. A high proportion of cases were females. The persons affected were mainly young adults, with some cases in their twenties. Thrombocytopenia is documented in most cases of thrombotic events. While the study did not establish any relationship between the cases and the vaccine, the EMA agreed to recommend the addition of special warnings and precautions in product data.[114]

Upon the recognition of thrombotic events, many European countries felt compelled to pause their vaccination programs with AZD1222. In the meantime, a group of researchers from Germany published a non-peer reviewed article where 9 of their patients have presented with thrombotic complications after vaccination with AZD1222.[115] Shortly after, the same group published the extended results of their 11 patients that show similar findings.[116] In this article, of the 11 of their patients, 9 were women, with a median age of 36 years (range: 22 to 49). These patients have presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. 5 of the 10 patients had more than one thrombotic event. These events occurred between 5 and 16 days after vaccination with AZD1222. Of the patients with one or more thrombotic events, 9 had CVST, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thrombotic events. Six of these patients have died. All the patients presented with moderate to severe thrombocytopenia (range: 9,000 to 107,000). Five patients had confirmed DIC. None of the patients had received heparin before the symptom onset. Nine of the 11 patients tested strongly positive for anti-platelet factor-4 (PF4)/heparin antibodies by immunoassay; all 9 patients tested strongly positive in the platelet activation assay in the presence of PF4 independently of heparin. Interestingly, platelet activation was inhibited by high concentrations of heparin, Fc receptor-blocking monoclonal antibody, and intravenous immunoglobulin in this study. Furthermore, although their clinical information was not available, there were 19 additional patients whose serum samples that were sent to the researcher's reference laboratory exhibited similar results. The authors called this syndrome vaccine-induced thrombotic thrombocytopenia (VITT) to avoid confusion with HIT.

Meanwhile, another similar report has been published by a Norweigen group. These 5 patients were health care workers who presented with venous thrombosis and moderate to severe thrombocytopenia, 7 to 10 days after receiving the first dose of the AZD1222. Their ages were in the range of 32 to 54 years. Four of them were females. All the patients had high levels of antibodies to PF4-polyanion complexes. However, they had no previous exposure to heparin. Four had CVST and 1 had splanchnic-vein thrombosis. These 5 cases occurred in a population of more than 130,000 vaccinated individuals. The authors concluded that these findings correspond to a new phenomenon termed as VITT.[117]

These results of the publications found wide circulation across the news media and scientific communities globally. While some countries totally suspended the use of AZD1222, others restricted their use to under 55-70 years of age. Some countries decided to continue vaccinations with precautions such as the ones published by the United Kingdom, Germany and Canada.[118-120]

Shortly after the reports of AZD1222, FDA and Centers for Disease Control and Prevention (CDC) of the United States announced 6 reported cases of CVST in individuals after receiving the Ad26.COV2.S vaccine. In these cases, the CVST was seen in combination with thrombocytopenia. All 6 cases occurred among women between the ages of 18 and 48, and symptoms occurred 6 to 13 days after vaccination with Ad26.COV2.S vaccine. These 6 cases were detected among a population of more than 6.8 million who have been vaccinated with Ad26.COV2.S. Out of an abundance of caution, the CDC and FDA recommended an initial pause for the use of Ad26.COV2.S vaccine.[121] After that, Ad26.COV2.S vaccinations have been paused by the producer company.

Following this, another report of a 48 year-old female patient has been published. This patient presented with extensive splanchnic-vein and CVST with severe thrombocytopenia and DIC after Ad26.COV2.S vaccination. The screening test for antibodies against PF4–heparin by latex-enhanced immunoassay was negative in this patient. However, the results of enzyme-linked immunosorbent assay for antibodies against PF4–polyanion was strongly positive. The authors mentioned that rare occurrence of VITT can be related to Ad26.COV2.S vaccine.[122]

Researchers from the U.K. also have published their observations recently. In this report a total of 23 patients were identified, 22 patients presented with acute thrombocytopenia and thrombosis and 1 patient presented with isolated thrombocytopenia and bleeding symptoms after vaccination with AZD1222. The thrombotic events were primarily CVST cases. These patients were 21 to 77 years of age and 13 of them were females. Gender differences in platelet activation responses and their inhibition by aspirin have been previously reported.[123] Testing for antibodies to PF4 was positive in 22 patients and negative in 1 patient.[124]

When all these reports are taken into account, it seems that the pathophysiologic mechanism of VITT links to the endogenous production of antibodies targeting PF4. These antibodies cause neutralization of endogenous glycosaminoglycans, leading to propagation of coagulation cascade and causing thrombotic complications.[125,126] However, this is different from classical HIT because the antibodies that are produced in VITT are produced without previous exposure to heparin.

The association of anti-heparin platelet factor 4 antibodies and the role of platelet factor 4 in some of the COVID-19 vaccine related thrombotic complications with thrombocytopenia

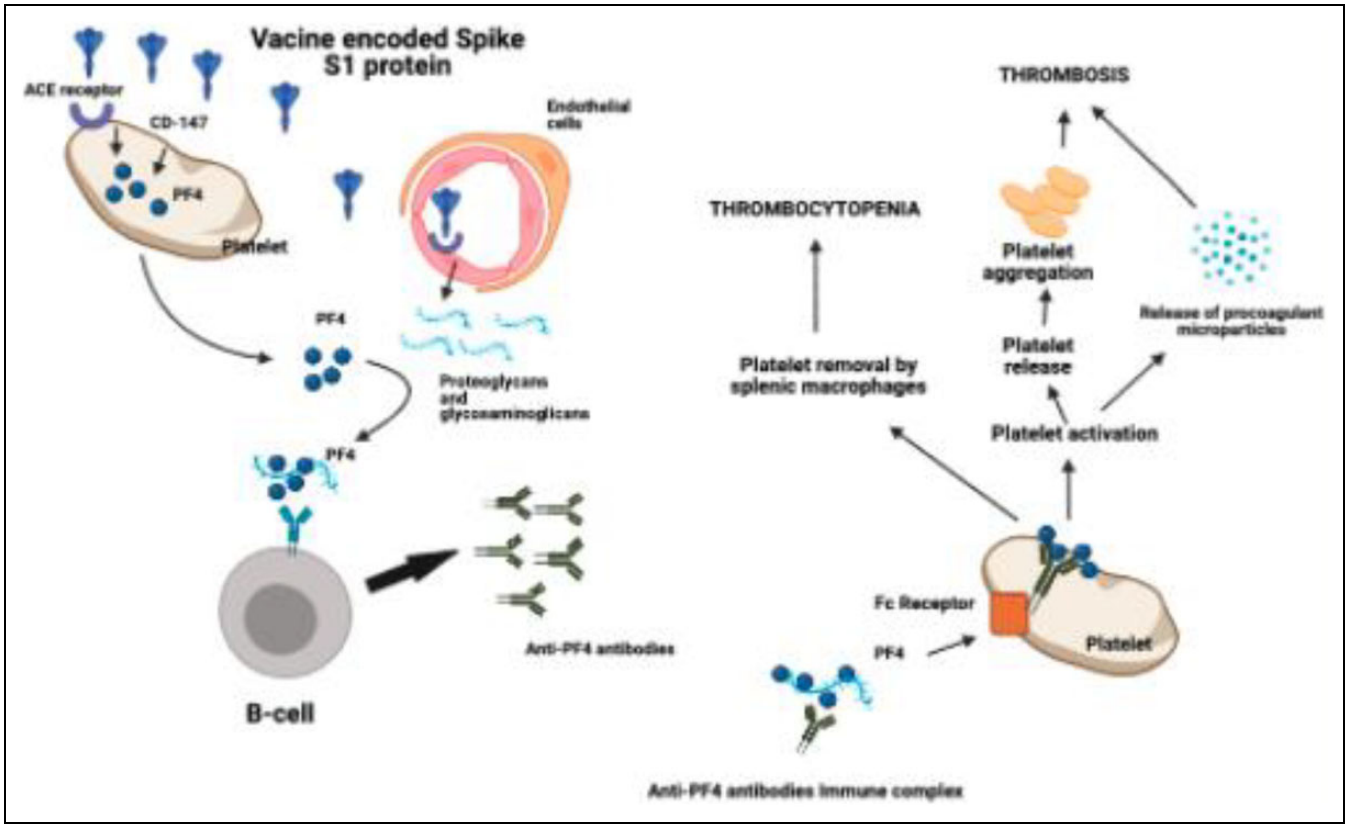


**Figure 1.** Proposed mechanisms of vaccine induced mobilization of platelet factor 4 and perturbation of endogenous glycosaminoglycans/proteoglycans leading to the generation of apparent anti-glycosaminoglycan PF4 antibodies. Some of the vaccine encoded spike proteins may target endothelial lining, triggering the release of glycosaminoglycans resulting in the shedding of these polyanions. Similarly, spike proteins may directly or indirectly activate platelets and release platelet factor 4 resulting in the formation of complexes with polyanions including glycosaminoglycans. These new antigens may mediate the formation of anti-glycosaminoglycan/PF4 antibodies. Such antibodies may trigger activation of platelets and subsequent pathophysiologic effects including thrombocytopenia.

is a major focus to understand this presumed autoimmune response. It is likely that encoded spike proteins generated by some of the vaccines may trigger platelet activation via multiple mechanisms resulting in increased levels of PF4 in circulation. Additionally, the encoded spike protein and associated inflammatory responses may induce endothelial damage and shedding of glycosaminoglycans. This may result in the formation of PF4 complexes with endogenous glycosaminoglycans such as heparan sulfate and other anionic polymers. These complexes trigger the generation of antibodies which may have similar effects on platelets as the conventional anti-heparin platelet factor 4 antibodies. Additionally, the inflammatory responses resulting from vaccination may also trigger the shedding of endothelial glycosaminoglycans which can complex with PF4. The occurrence of anti-heparin PF4 antibodies in otherwise heparin naive patients has been reported previously.[79,127] Although current research is ongoing to understand the mechanisms involved in the generation of the anti-heparin platelet factor 4 antibodies after vaccination, a definitive causal relationship has yet to be demonstrated (Figure 1).

There is a lot of coverage in the popular media and news about the thrombotic events related to the COVID-19 vaccines. These reports may cause the public to question the efficacy and safety of all vaccines, leading to vaccine hesitancy. The incidence of this constellation of findings appears to be extremely low following either vaccine. Additionally, the overwhelming benefits of vaccines against COVID-19 is proven. However, although a causal association has not yet been confirmed, it is important to acknowledge that there may be an association with a rare but serious adverse event related to thrombosis and thrombocytopenia. Furthermore, rapid identification of this rare syndrome may provide important therapeutic implications when it is needed.

Finally, the abrupt reactions to the AZD1222 vaccine left certain populations who had received their first dose, but not the second dose, in a challenging situation. What should be done with the second dosage remains an open question. Some countries urged these recipients to proceed with the second dose of AZD1222, while others, like France, announced that they can finish their vaccine scheme with a different vaccine. To investigate the combination of different vaccines, researchers in the University of Oxford launched a clinical trial (Com-Cov vaccine trial) where they are investigating the combinations of AZD1222 and BNT162b2 vaccines.[128]

Considering how vital the success of vaccination programs are for the fight against COVID-19, it is critical to conduct additional studies on the combination of different vaccines.

## Management of VITT

In summary, VITT is a new syndrome characterized by 1) thrombosis, particularly at unusual sites including CSVT/splanchnic thrombosis; 2) mild to severe thrombocytopenia; and 3) positive PF4-heparin ELISA and platelet activation assays. It is described in the first 16 days of vaccination with AZD1222 or Ad26.COV2.S vaccines. Patients in these reports were primarily younger than 55 years, and were mostly females. None had received heparin earlier and few had other known risk factors for thrombosis. Many of the patients were critically ill by the time thrombosis and thrombocytopenia were discovered, and up to one-half of the reported patients died.[129]

Patients with severe, recurrent, or persistent symptoms, particularly intense headache, abdominal pain, nausea and vomiting, vision changes, shortness of breath, and/or leg pain and swelling, either persisting or beginning 4 to 20 days following vaccination, should be evaluated urgently for an underlying VITT. Initial work-up should include CBC with platelet count, imaging for thrombosis based on symptoms, D-dimer and fibrinogen assays and PF4/heparin ELISA which were reported as positive in all cases. Blood should be drawn for a confirmatory PF4 platelet activation assay such as serotonin release assay, P-selectin expression assay, or heparin induced platelet aggregation (HIPA) assay. Patients with severe symptoms and/or positive imaging in addition to low platelet counts and high D-dimers can be considered to have VITT and started on treatment while awaiting ELISA results. The incidence of a positive ELISA across populations of vaccinated or post-COVID patients is unknown, and also the degree of ELISA positivity correlated with the risk. Low levels of fibrinogen and extremely high D-dimer levels suggest that DIC should also be considered as a part of the VITT syndrome. Microangiopathy with red cell fragmentation and hemolysis has not been a feature of reported cases. Patients with isolated thrombocytopenia and continued absence of thrombosis may have post-vaccine ITP and not VITT as confirmed by a negative PF4 ELISA.[129]

Treatment of VITT is similar to that of severe HIT, including; a) IVIG 1 gram/kg daily X 2 days, b) non-heparin anticoagulation, chosen based on the clinical status and organ function of the patient (Parenteral direct thrombin inhibitors [argatroban or bivalirudin provided the baseline aPTT is normal], direct acting oral anticoagulants, fondaparinux, or danaparoid), c) being aware of low fibrinogen levels or bleeding which may be associated with VITT, and should not absolutely preclude anticoagulation, particularly if platelets are >20,000/uL or increasing following IVIG initiation and d) avoidance of platelet transfusion.[129]

## Conclusion

After a year of living with the crippling impacts of the pandemic at a global scale, availability and wide scale distribution of vaccines finally provided the much needed hope for recovery and return to normalcy. Overall, vaccines have been shown to be highly effective and safe. Researchers are continuing to investigate any concerns in order to put to rest any remaining doubts and eliminate side effects such as in the AZD1222 or Ad26.COV2.S cases. While we have come a long way in our understanding of COVID-19, our knowledge continues to evolve every day, and it will continue to do so for years to come. Therefore, it is important to continue the ongoing research on the SARS-CoV-2 virus, vaccine development and impacts of the vaccines. To date, hundreds of millions of doses of vaccines have been administered around the world, and as the momentum continues, we are going to succeed in seeing the end of this pandemic. Recognizing the importance of the benefits of available vaccines and despite the rare incidences of thrombotic complications with some of the vaccines the US FDA and EMA have lifted the temporary pauses on their use. It is reassuring to note that pharmacovigilance and long-term safety programs with each of the currently used vaccines are in place which will be helpful in guiding the safer use of different vaccines based on population stratification and other demographic factors. Since the benefits of vaccination far outweigh the reported risks associated with thrombosis, the vaccination programs should continue despite such risks.

### Acknowledgments

The authors of this manuscript would like to thank Drs. Mark Ligocki, Debra Hoppensteadt, Fakiha Siddiqui, and Ahmed Kouta for their valuable input in preparing this manuscript. We would also like to thank Ms. Erin Healy-Erickson for her skillful assistance in finalizing this communication.

### 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.

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