Section A-Research paper

Possible Adverse Effects of Covid-19 Vaccines

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Abstract

Background: COVID-19, apart from becoming the greatest threat to global public health of the century, is being considered as an indicator of inequity and deficiency of social advancement. As is implied in the name COVID-19, 'CO' stands for 'corona,' 'VI' for 'virus,' and 'D' for disease, and 19 represents the year of its occurrence. During the pandemic, various COVID-19 treatment strategies have been developed and widely introduced to clinical practice. Antimalarials and some antivirals, such as lopinavir and ritonavir, which had been used at the early stages of the pandemic, were later found to be ineffective and/or associated with risks to patient health. To date, an effective curative therapy that can be used in a wider population is still lacking. Therefore, only symptomatic and pathogenesis-based treatments are available, even for patients with moderate to severe disease. In such a situation, the most promising strategy for overcoming the pandemic is vaccination of the entire population. Vaccines represent one of the most critical advances in medicine and are the most effective method to prevent morbidity and mortality associated with infections. However, unlike antimicrobial agents used to treat infected persons, vaccines are applied to healthy subjects to prevent infections; therefore, adverse effects acquire great relevance. Nevertheless, adverse effects do not outweigh the indisputable advantages vaccines offer to humanity by preventing diseases that constitute a significant economic, social, and familial burden. In this manner, informing individuals, families, and communities of the characteristics of vaccines makes the risk–benefit of each of the vaccines more familiar, doubtlessly contributing to the population's health

Keywords: Reactions of Covid-19 Vaccines

Introduction

Pandemics in general are not merely serious public health concern, rather these trigger disastrous socio-economic and political crises in the infected countries. The coronavirus disease 2019 (COVID-19) is one of the biggest public health threats in the 21st century. Nearly every country in the world has been affected by COVID-19**.(1)**

COVID-19, apart from becoming the greatest threat to global public health of the century, is being considered as an indicator of inequity and deficiency of social advancement. As is implied in the name COVID-19, 'CO' stands for 'corona,' 'VI' for 'virus,' and 'D' for disease, and 19 represents the year of its occurrence **(2)**

In late December 2019, an outbreak of a mysterious pneumonia characterized by fever, dry cough, and fatigue, and occasional gastrointestinal symptoms happened in the Huanan Seafood Wholesale Market, in Wuhan, Hubei, China which Live animals like bat, frog, snake, bird, marmot and rabbit are frequently sold [1] The initial outbreak was reported in the market in December 2019 and involved about 66% of the staff there**.(3)**

The market was shut down on January 1, 2020, after the announcement of an epidemiologic alert by the local health authority on December 31, 2019. However, in the following month (January) thousands of people in China were attacked by the rampant spreading of the disease. Furthermore, the disease traveled to other countries and has been categorized as a pandemic by the World Health Organization . The pathogen of the outbreak was later identified as a novel beta-coronavirus, named 2019 novel coronavirus (2019-nCoV) and recalled to our mind the terrible memory of the severe acute respiratory syndrome (SARS-2003, caused by another beta-coronavirus) **.(4)**

Coronavirus is a single stranded RNA virus surrounded by an envelope with a diameter ranging from 80 to 120 nm. Coronaviruses belong to a large diverse family of viruses. These can be categorized into four genera namely, α-, β-, γ-, and δ. All the previously discussed coronaviruses responsible for worldwide spread of pandemic, namely SARS, MERS-CoV and SARS-CoV-2 are β-coronaviruses**. (5)**

There are hundreds of viruses that belong to the coronavirus family. However, only six (229E, NL63, OC43, HKU1, SARS-CoV and MERS-CoV) have been reported to cause mild to severe respiratory tract infections in humans **(6)** Among them are severe acute respiratory syndrome coronavirus (SARS-CoV) reported in November 2002 and middle east respiratory syndrome coronavirus (MERS-CoV) reported in September 2012, which emerged in human population from animal reservoirs and caused severe respiratory illness with high mortality rates **(7,8)**

Once again, a novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged, and caused an infectious disease called coronavirus disease 2019 (COVID-19) **(9)**

The emergence COVID-19 in has caused a large global outbreak and is a major public health issue. This virus is highly infectious and can be transmitted through droplets and close contact. The human to the human spreading of the virus occurs due to close contact with an infected person exposed to coughing, sneezing, respiratory droplets or aerosols. These aerosols can penetrate the human body (respiratory system) via inhalation through nose or mouth. The time between catching the virus and beginning of symptoms of the disease is known as incubation period. For COVID-19, it ranges from 1-14 days but most commonly around five days. **(10).**

Vaccines represent one of the most critical advances in medicine and are the most effective method to prevent morbidity and mortality associated with infections. However, unlike antimicrobial agents used to treat infected persons, vaccines are applied to healthy subjects to prevent infections; therefore, adverse effects acquire great relevance. Nevertheless, adverse effects do not outweigh the indisputable advantages vaccines offer to humanity by preventing diseases that constitute a significant economic, social, and familial burden. In this manner, informing individuals, families, and communities of the characteristics of vaccines makes the risk–benefit of each of the vaccines more familiar, doubtlessly contributing to the population's health .

Adverse reactions of vaccines

The vaccine also has adverse reactions such as redness, swelling, muscle pain, and fever.38, 39 The strategic objectives of the COVID-19 vaccine roadmap formulated by WHO include a series of preferred and most basic requirements such as vaccine safety and effectiveness.40 The preferred requirements for safety/reactogenicity include "safety and reactogenicity sufficient to provide a highly favorable benefit/risk profile in the context of the observed vaccine efficacy and only mild, transient related to adverse vaccination events without serious adverse events**". (11)**

The most basic requirements for safety/reactogenicity include the benefits of vaccines outweigh the potential safety hazards. The long-term results were a safety that is sufficient to provide highly favorable benefits/risk characteristics in the context of the observed vaccine efficacy and immunogenicity. There were no serious adverse events related to vaccination. The preferred requirements for effectiveness include the protection effectiveness in the population is at least 70%, and the same is true for the elderly. If it is an outbreak treatment, the protective effect must appear within two weeks and last for at least one year. The most basic requirements include the population's protective effect is at least about 50% for at least six months**.(12)**

1-mRNA vaccines

For the 2 mRNA vaccines, the second dose was associated with more adverse effects than the first dose. A higher rate of systemic events was reported by younger vaccine recipients (aged 16–55 years) than those older than 55 years, which may be due to a more robust immunogenic response in younger persons.Evaluation of the vaccines vs placebo (normal saline) showed a higher incidence of mild local adverse effects such as pain, heat, swelling, and redness. The vaccines were also associated with other

systemic adverse effects such as fever, fatigue, arthralgias, myalgias, and headache. These adverse effects usually developed within 1 to 2 days of vaccination [**123].**

In initial trials, the localized symptoms were mild to moderate in severity and lasted 1 to 2 days. Moderate to severe systemic symptoms, such as headache, myalgia, arthralgia, and fatigue, also lasted 1 to 2 days. More local reactions were seen among the vaccine group than the placebo group. The most common localized symptom was pain at the injection site, which was seen within 1 week of vaccination .Anaphylaxis and edema of the labial, facial, and glossal areas were among the adverse events noted **(13).**

2-Oxford/AstraZeneca ChAdOx1 nCoV-19 Vaccine (AZD1222)

Efficacy and safety results for AZD1222 have been documented in 4 randomized clinical trials in the UK, South Africa, and Brazil. Overall, the vaccine was safe across all 4 studies, and serious adverse events were evenly distributed among all study groups. A total of 168 serious adverse events were reported among 79 recipients of AZD1222 and 89 recipients of saline control . One case of transverse myelitis was reported 14 days after the second dose of AZD1222; this was viewed as possibly related to vaccination, and a diagnosis of an idiopathic, short-segment, spinal cord demyelination was made. In South Africa, 1 patient had a fever higher than 40°C 2 days after vaccination, but the patient recovered quickly **(14).**

In another study, laboratory tests in 11 patients in Austria and Germany indicated either thrombocytopenia or thrombosis after being vaccinated with AZD1222 **(15).**

3-Johnson & Johnson (Janssen) Ad26.COV2.S

After 6 recipients were diagnosed with cerebral venous sinus thrombosis and thrombocytopenia, the FDA and the Centers for Disease Control and Prevention (CDC) recommended a pause in the administration of Janssen vaccines). In Europe, reports of similar thrombotic events have been observed primarily among women younger than 60 years after receiving the AstraZeneca AZD1222 vaccine **(16).**

4-Sputnik V

The Gamaleya National Center of Epidemiology and Microbiology in Moscow was already devising prototypes of Sputnik V when the WHO declared COVID-19 a pandemic . In September 2020, researchers published results from phases I and II of an open, nonrandomized trial of 76 participants **(17).**

All participants were reported to have developed antibodies against SARS-CoV-2. Pain at the injection site, asthenia , headache , hyperthermia , and muscle pain were among the most common adverse events. Serious adverse events were not observed .The rapidity and lack of transparency in the development of the Sputnik V vaccine have been criticized, however **(18).**

5-Sinovac & Sinopharm

Sinovac& Sinopharm are an inactivated virus vaccine that was one of the earliest to join the COVID-19 vaccine trial line In April 2020 .In general, the bad effects that arise can vary, are generally mild and temporary and do not always exist depending on the condition of the human body.

Sinovac was well received in all age groups (18–50 years) without severe adverse effects. The most common post-vaccination bad effects were itching and pain in ,followed by systemic bad effects, namely fatigue/malaise and muscle pain/myalgia .A similar vaccine. Sino-pharm, was tested in China and did not report fatigue, headache, fever, and muscle aches**.**

Autoimmune and autoinflammatory conditions after COVID-19 vaccination

The pandemic's influence has boosted vaccine development, allowing them to be manufactured in record time. As a result, many vaccines with unique and promising modes of action have been developed. However, the quick deployment has raised several issues, including their safety, which could be linked to the dose given and the age of the patients (occurring before 55 years of age in most cases) **(19).**

We report patients who had autoimmune and autoinflammatory diseases, either for the first time or as a relapse. The most common diseases linked to immunization were thrombocytopenia, myocarditis, GBS, nephropathy, and thyroid disorders. It is remarkable since some of these diseases are usually triggered by infections and other vaccines . It suggests similar immunopathogenic mechanisms between vaccines and infectious agents as triggering factors of Ads **(20).**

This hypothesis could be supported through the *anti*-idiotype immune response, which shows that antibodies against a specific antigen can trigger the production of second particular antibodies against the first ones. Surprisingly, the second antibodies may be capable of binding to receptors that the initial antigen may attach to. This is significant since many autoimmune or autoinflammatory reactions elicited by COVID-19 vaccinations have previously been reported with vaccines whose principal immunopathogenic mechanism is the *anti*-idiotype immune response. SARS-CoV-2 might trigger ADs through different mechanisms, including molecular mimicry . Several studies have demonstrated that the history of past infections can alter the reactogenicity of mRNA vaccines through a cross-reactivity mechanism . However, greater reactogenicity may confer higher protection but could generate more adverse events. (**21)**

Remarkably, patients with ADs are not at increased risk of adverse events associated with vaccination , possibly due to the effect of immunomodulatory drugs on vaccine immunogenicity.
Although RNA-based vaccines focus on synthesizing antigens that facilitate immunogenicity, the mRNA may bind to pattern recognition receptors (PRRs) in the cytosol or on the endosomes before translation**. (22).**

Rare adverse effects of COVID-19 vaccines

1-Cardiac effects

A-Myocarditis/perimyocarditis

The mRNA vaccine (BNT162b2 and mRNA-1273) has shown excellent reliability to reach the global vaccine demand against COVID-19. However, few myocarditis/perimayocarditis have been reported in young children adults from different countries. From 19 December 2020 to 11 June 2021, 1226 cases of myocarditis were reported to Vaccine Adverse Event Reporting System. The excessive risk was about 2.7 (1 to 4.6) events per 100,000 persons. Potential mechanisms of post-vaccination myocarditis or pericarditis include hormonal differences, mRNA immune reactivity, and antibody cross-reaction with myocardial proteins although the exact mechanism remains elusive**. (23).**

The cases are mild and temporarily exist but can cause severe effects on adolescents. Pleuritic chest pain, dyspnoea, or palpitations are the symptoms that can be noticed especially in younger children with myocarditis besides, epigastric pain, profuse sweating, tachycardia, hypotension can also be observed in some cases .According to multiple case reports, most of the symptoms for myocarditis arise within 1–4 days after the first or second dose**,** more often after the second dose. Younger males, 12–29 years, are predominantly affected. Cardiac magnetic resonance imaging was an effective tool for the diagnosis of myocarditis. Elevated troponin level was reported in almost every case; in some cases, c reative protein and creatine kinase, CK-MB, and B-type natriuretic peptide levels were also reported higher. Different drugs were introduced to treat and elevate the symptoms of myocarditis. Aspirin, colchicine, ibuprofen, beta-blockers, steroids or corticosteroids, intravenous anti-inflammatory drugs were used for the recovery of patients . **(24).**

B- Arrythmia & ECG changes

The current systematic review and meta-analysis showed that the IR of cardiac arrhythmia post-COVID-19 vaccination is rare and ranges between 1 and 76 per 10,000. mRNA vaccines, including Moderna and Pfizer, were associated with a higher IR of arrhythmia than vector-based vaccines. On the other hand, inactivated vaccines, such as CoronaVac and Sinopharm, showed the lowest IR of arrhythmia**.**
the results of individual studies demonstrated that arrhythmia was one of the largest relative risks associated with COVID-19 vaccines, besides thromboembolic events, sexual organ reactions, ocular, gastrointestinal, constitutional, hemorrhage, coagulation, and other cardiovascular events. However, arrhythmia was not reported among the ten most frequent cardiovascular events attributed to the Moderna, Pfizer, or Johnson & Johnson vaccines. On the other hand, they showed that the Johnson & Johnson vaccine was associated with the lowest RR of arrhythmia when compared with Moderna and Pfizer**. (25).**

Regarding the comparison between the Pfizer COVID-19 vaccine and other vaccines, AbRahman et al. conducted a controlled case-series study, comparing SinoVac, Pfizer, and AstraZeneca. Their findings showed that among the patients who developed new-onset arrhythmia, 60.7% received the Pfizer COVID-19 vaccine, 35.3% received SinoVac, 3.9% received AstraZeneca, and 0.2% received other vaccines. The event rate of arrhythmia per 1 million vaccinated persons was 95.47, 51.76, and 26.92, following Pfizer, Sinovac, and AstraZeneca vaccines, respectively. However, the IRR results showed that those who received SinoVac had the lowest IRR of arrhythmia compared to Pfizer and AstraZeneca**.** Most of these patients were over 60 years old (66.5%). About 55.1% of the patients received the first dose of the vaccine, and 44.9% experienced arrhythmia after the second dose. Almost half of the patients already had hypertension, 16% had diabetes, and 12% had other heart diseases. They concluded that they could not highlight a significant association between cardiac arrhythmia and COVID-19 vaccines; **(26).**

The Case Series Drug Analysis Print published by Pfizer-BioNTech for their COVID-19 vaccine as of May 28, 2021, reported a total of 2342 cardiac AEs, among which 1098 events were classified as palpitations, 16 events were classified as acute myocardial infarction, 38 events as arrhythmia, 24 events as cardiac failure, 46 events as angina pectoris, 32 events as sinus tachycardia, 63 events as cardiac flutter, 62 events as cardiac arrest, 108 events as atrial fibrillation, and 466 events as tachycardia**.** The rhythm disorders, as reported by AstraZeneca for their COVID-19 vaccine, included 1763 events of palpitations, 6 events of unstable angina, 8 events of supraventricular tachycardia, 8 events of tachyarrhythmia, 21 events of extrasystoles, 34 events of sinus tachycardia, 43 events of arrhythmia, 78 events of atrial fibrillation, and 622 events of tachycardia. In terms of ECG changes associated with COVID-19 vaccines, Truong et al. enrolled 139 adolescents and young adults with 140 episodes of suspected myocarditis who received Pfizer, Moderna, and Janssen vaccines. Their findings showed that 97 patients presented with ECG changes and arrhythmias, including ST- or T-wave changes/elevation (97.9%), complete heart block (0.7%), first-degree atrioventricular block (0.7%), premature atrial contractions (0.7%), atrial tachycardia (0.7%), low-voltage QRS (3.6%), and non-sustained ventricular tachycardia (5%) **(26).**

2-Neurological effects

Vaccination induces a series of immunological events which may cause neurological problems, for example, demyelinating diseases, epileptic seizures, Guillain-Barre syndrome, and stroke. The most common neurological symptoms after the vaccination include dizziness, headache, pain, muscle spasms, myalgia, and paresthesia, which are usually acute and transient. Furthermore, in limited studies, tremor, diplopia, tinnitus, dysphonia, and seizures were seen after COVID-19 vaccination. In a trial of the Pfizer–BioNTech (BNT162b2) mRNA vaccine, 7 out of 37,000 participants developed Bell's palsy, although the rate of the disease was not higher than expected in the general population **(27).**

Stroke

Stroke is a major cause of death and disability globally. It can be classified into two main categories of ischemic and hemorrhagic stroke, the latter has higher mortality than the former.

Ischemic stroke after COVID-19 vaccination

In ischemic stroke, a region of the brain is dispossessed of blood flow which can be due to thrombosis of an artery or, in rare instances, a vein. Thrombosis can occur in the vessels following COVID-19 vaccination. They are usually seen in the context of VITT. These cases were mostly diagnosed following ChAdOx1 nCoV-19 vaccine, especially with the involvement of the middle cerebral artery (MCA). The emergence of persistent or unusual neurological symptoms after receiving the COVID-19 vaccines should urgently be evaluated for VITT with neuroimaging techniques and laboratory tests **(28).**

Hemorrhagic stroke after COVID-19 vaccination

Hemorrhagic strokes occur when a blood vessel ruptures. ICH and subarachnoid hemorrhage (SAH) can occur after COVID-19 vaccination, which can be primary or secondary to venous thrombosis.While ICH after COVID-19 vaccination can occur in the context of VITT, Silva et al. described primary hemorrhagic

stroke following ChAdOx1 nCoV-19 vaccination in a patient without thrombocytopenia, coagulation disorder, or coagulation risk factors. Argument for such a causal relation is that arterial hypertension and ICH are complications of COVID-19 vaccination. More to the point, hypertension is an important risk factor of ICH. most of the cases were reported following administration of ChAdOx1 nCoV-19 vaccine and in people 30–57 years of age, 5–12 days after the vaccination**.(29).**

Cerebral venous sinus thrombosis after COVID-19 vaccination

CVST is a rare form of stroke occurring often in young and middle-aged women. Partial or complete occlusion of cerebral venous sinus system or its small-caliber draining veins leads to venous hypertension, localized parenchymal edema, raised intracranial pressure (ICP), infarction, and rarely ICH The most common manifestation of CVST is headache, which may be generalized or focal and is often progressive. CVST has been reported in COVID-19 patients and is paradoxically associated with thrombocytopenia This phenomenon can be explained by systemic platelet consumption and sequestration through agglutination triggered by COVID-19 vaccine immunization process, which may lead to thrombosis**.(30)**

CVST after vaccination mostly occurs with adenoviral COVID-19 vector vaccines, especially ChAdOx1 nCoV-19 vaccine; nonetheless, CVST may also occur following mRNA-based COVID-19 vaccines. CVST usually has a good prognosis. However, CVST after COVID-19 vaccination may follow a catastrophic course. The outcome for these patients may be poor due to refractory increased ICP; indeed, almost half of patients with CVT die within a few days and death often occurs following brain infarction often associated with ICH **(30)**

Guillain–Barre Syndrome

Post COVID-19 vaccination, rare neurological effects have been reported in a few patients. A 61-year-old man and an 82-year-old woman developed the Guillain–Barre Syndrome (GBS) post-vaccination with Pfizer and Moderna vaccines respectively. GBS is an inflammatory polyradiculoneuropathy disease affecting peripheral nerves and nerve roots, associated with viral infections.

In both cases, symptoms like difficulty in walking, weakness in extremities and muscles were common. In the 82-year-old lady, symptoms like body ache started after the first week of administration and worsened during the second week**. (31)**

Lumbar puncture and cerebrospinal fluid analysis confirmed the development of GBS. Intravenous immunoglobulin (IVIG) was given for treatment for up to 5 days, and after 3 days, improvement was observed in her. In the 61-year-old male, symptoms like weakness in proximal and upper extremities were reported 4 days after receiving the second dose of Moderna vaccine. His cerebrospinal fluid analysis and electrodiagnostic tests showed an acute demyelinating polyneuropathy. After 5 days of IVIG administration, his condition also improved**. (31)**

Transverse myelitis

Transverse myelitis is an demyeliting disease, linked to COVID-19 vaccines. It has been suggested that post-vaccination demyelination might be a trigger for the disease's expression, in people already predisposed towards it. Transverse myelitis can also appear as a result of viral infection, suggesting that viral antigens, present in the vaccine, or even the adenovirus itself can induce relevant immune responses. The most likely mechnanism is molecular mimicry and bystander activation of the immune system, leading to autoimmunity **(32)**

Bell's Palsy

Bell's Palsy appears to be a rare adverse event of mRNA vaccines. A potential mechanism is the activation of type I interferons, by the vaccine's mRNA and/or lipids, leading to lymphocyte activation and inflammation. Furthermore, IFNα seems to have the ability to breakdown myelin antigens, thus leading to neuropathy [108, 110]. The autoimmune responses may also result from molecular mimicry or bystander activtion of T cells **(33),**

3-Severe allergic reactions/anaphylaxis

The mRNA vaccines Moderna and Pfizer/BioNTech have been reported to cause life-threatening allergic reaction anaphylaxis in different countries, including the United States, the United Kingdom, and Singapore. In the United States, VAERS reported 108 cases and 175 cases of severe allergic reaction post-vaccination (in some cases first dose or second dose) of Moderna and Pfizer, respectively. 10 (from 108 cases) and 21 (from 175 cases) patients were determined as anaphylaxis from these cases. In the United States, it is determined that the rate of anaphylaxis for Pfizer and Moderna is 2.7 and 11.1 cases per million doses, respectively**. (34)**

The mRNA vaccines are carried by lipid nanoparticles that contain an excipient called PEG-2000 and polysorbate. There are some structural similarities between Polysorbate and PEG molecules.The cause of these rare adverse effects is unclear, but it has been postulated that the polyethylene glycol (PEG) in BNT62b2 and polysorbate-80 in mRNA-1273 could be the culprit**. (34)**

Several reports indicate that people with a history of an allergic reaction, PEG allergic, asthma, rhinitis, and urticaria are more prone to develop severe allergic reactions .From the 108 and 175 cases, 10 cases (9 with previous allergic history) and 21 (17 with previous allergic history) cases of anaphylaxis were found, respectively**. (34)**

Symptoms such as edema, globus sensation, rash, wheezing, flushing, breathlessness, throat closure, and swelling, and generalized urticaria were reported through various case studies. The onset of symptoms varies from minutes to hours; however, the median onset time post-vaccination was recorded about 7.5 min (actual range is 1–45 min) in Moderna and 13 min (actual range 2–150 min) in the Pfizer vaccine. The reported patients were administered with intramuscular injection of epinephrine as a treatment due to the life-threatening nature of anaphylaxis**.(35)**

Ocular adverse effects

Vaccines have been reported to induce ocular side effects, including conjunctival and eyelid reactions, optic neuritis and intraocular inflammation. Furthermore, live attenuated vaccines may cause ocular infection from the organisms derived, especially in at-risk groups, including the immunosuppressed .The adjuvants included in COVID-19 mRNA vaccines stimulate innate immunity through endosolic or cytoplasmic nucleic acid receptors including Toll-like receptors (TLRs). Several autoimmune diseases, particularly connective tissues diseases, are associated with an altered nucleic acid metabolism and processing, which may trigger an immune response following immunization. the ocular adverse effects reported were Bell's/facial nerve palsy, central venous sinus thrombosis and thrombosis, acute anterior uveitis, acute macular neuroretinopathy, corneal graft rejection, anterior scleritis , panuveitis, posterior uveitis, cranial nerve palsy (excluding Bell's/facial nerve palsy), central serous chorioretinopathy, central retinal vein occlusion, bilateral multifocal choroiditis, episcleritis, intermediate uveitis, paracentral acute middle maculopathy, subretinal fluid and bilateral optic neuritis. The reported entities appear to overlap with the ocular manifestation reported in patients infected with COVID-19, suggesting a common pathway (possibly TLR) between virus and vaccine-mediated immune response in humans. **(36)**

4-Glomerular adverse effects

Since mass-vaccination campaigns began in January 2021, the incidence of vaccine-associated glomerular disease has increased. Symptoms of recurrent glomerular diseases or new glomerular diseases have appeared, especially after administration of the mRNA vaccines. **(37)**

The pathogenesis behind vaccine-associated glomerular disorders is not clearly understood. However, an immunogenic response to vaccines has been noted as a possible cause. Minimal change disease, anti-glomerular basement membrane disease, membranous glomerular disease, and immunoglobulin A nephropathy are some of the glomerular lesions observed after vaccination. Some case reports have described patients with gross hematuria after vaccination who were later found to have immunoglobulin A nephropathy**. (37)**

The majority of vaccine-related cases were typically seen within 1 to 3 weeks after vaccination. Management of the glomerular disease must be on a case-by-case basis depending on the severity and remission status, because the benefits of vaccination outweigh the rare risk of glomerular disease**. (38)**

5-Vaccine-induced immune thrombotic thrombocytopenia

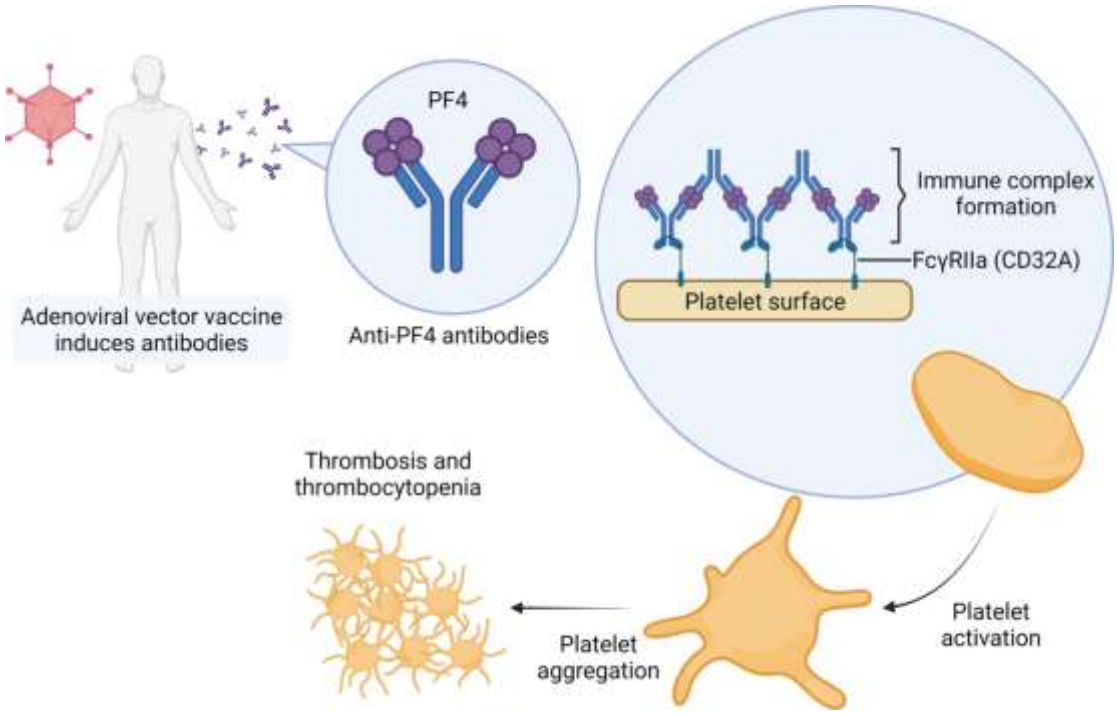
Followed by injection of adenoviral vaccines including Oxford–**AstraZeneca's** ChAdOx1 and **Janssen's** Ad26.COV2.S, there have been reports of rare SAEs such as thrombosis and thrombocytopenia syndrome. These events have been called vaccine-induced immune thrombotic thrombocytopenia (VITT) and are characterized by an atypical presentation of thrombotic events such as cerebral venous sinus thrombosis and splanchnic vein thrombosis . The frequency of VITT associated with the first dose of ChAdOx1 was estimated to be 8 to 38 cases per million doses mainly in women aged < 50**. (39)**

There are **several possible mechanisms** of VITT. One possible explanation is that the local inflammatory mediators such as vasodilators and cytokines enter the bloodstream, induce a short-lived systemic inflammatory response syndrome and lead to SAEs. This explanation assumes the same mechanisms as COVID-19 related syndromes. However, this could not explain why thrombosis is more frequent in adenoviral vaccines and not in other vaccines**.** Another group of researchers claimed that vector-based vaccines could generate alternatively spliced spike proteins that are secreted to the systemic circulation, where they cause thrombosis. This explanation is called vaccine-induced COVID-19 mimicry syndrome. However, spike proteins are also found in the sera of recipients of non-vector-based vaccines such as mRNA-1273. While the above studies offer possible explanations, they lack critical and direct evidence**. (40)**

Recent studies suggest a potential mechanism of VITT reminiscent of heparin-induced thrombocytopenia (HIT). HIT is a complication of heparin treatment that usually occurs 5 to 10 days after heparin exposure. It is characterized by venous thromboembolism and thrombocytopenia. After heparin exposure, the negatively charged heparin binds to the positively charged platelet factor 4 (PF4), forming an epitope and resulting in the production of anti-PF4 antibodies. Anti-PF4 antibodies form an immunocomplex with PF4 and bind to the Fc receptor of platelets, in turn activating the platelets. The activated platelets release more procoagulant proteins and cytokines including PF4. Uncontrolled platelet activation and aggregation lead to thrombosis and subsequent platelet clearance from the circulation leads to thrombocytopenia **(40)**

Similar to HIT, VITT is associated with IgG antibodies against PF4 . However, the anti-PF4 antibodies in VITT target a different epitope from those in HIT. VITT usually occurs later than HIT, ranging from 5 to 30 days (commonly **10** to **16 days**) following vaccination. It is not clear how anti-PF4 antibodies are induced in VITT, but researchers have proposed that the adenoviral vector in the vaccine plays a role. Same as heparin, the viral coat of the adenoviral vector is negatively charged and was found to form stable complexes with PF4. In addition, Baker et al. found a positive relationship between the negative charge on the viral coat and the frequency of thrombosis **(41)**

Taken together, this evidence suggests that the mechanism of VITT might include two steps. In the first step, the viral proteins in the vaccine components form complexes with PF4 and form epitopes that can be recognized by the immune system. Consequently, anti-PF4 antibodies are induced, in turn forming immune complexes with PF4 and binding with the Fc receptor on the surface of the platelet, leading to platelet activation, aggregation, and VITT 5 to 20 days after vaccination.The treatment method for Vaccine-induced thrombotic thrombocytopenia (VITT) is almost similar to the HIT. Any administration of Heparin or platelet transfusion should be stopped. Possible treatment methods are high doses of intravenous immunoglobulins (IVIG), non-heparin-based anticoagulants, corticosteroid administration, and plasma exchange. After clinical stabilization, oral anticoagulants such as apixaban, rivaroxaban can be given**. (42)**



(Fig)1 Potential mechanism of VITT. After vaccination, the viral proteins in the vaccine components might bind with PF4, thereby forming epitopes that can be recognized by the immune system and inducing the generation of anti-PF4 antibodies. Anti-PF4 antibodies form immune complexes with PF4 and bind with the Fc receptor on the surface of the platelet, leading to platelet activation and aggregation, and finally VITT 5 to 20 days after vaccination.

Potential molecular mechanisms of the adverse events

COVID-19 vaccines offer an opportunity to end the current global pandemic, with the approved vaccines eliciting sufficient immune response while being safe. Despite the different platforms used, all vaccines encode SARS-CoV-2 spike protein that is being recognized by the immune system forming anti-SARS-CoV- 2 IgG antibodies **(43).**

The rapid research and manufacturing process, in order to immediately confront the pandemic, raised concerns, especially regarding the safety profiles of the mRNA and viral vector vaccines.
mRNAs technology, despite being new, has some advantages over other platforms. Some of the advantages of mRNA-based vaccines include the fast-track manufacturing process, the inability of mRNA to integrate to the host cell's genome, reduced contamination issues, biodegradability, and elicitation of robust humoral and cellular immunity, thus acting concomitantly as both an immunogen and an adjuvant. However, mRNA products present stability issues which might be considered a major obstacle for worldwide distribution. Furthermore, data for the extent of the trapped mRNA inside the LNPs are not currently available **(44)**

In terms of the adenoviral vaccines, viral vectors have the potential of targeted gene delivery to the cells that results in efficient immune responses. These vaccines can also induce a high level of antibody production and T cell activation. On the other hand, they contain a double stranded gene, encoding for spike protein and thus neither the integration of the viral DNA in the host's genome, nor the production of various spike protein fragments can be excluded as factors implicated in some of the reported side effects. mRNA vaccines can cause anaphylactic and allergic reactions with the main culprit being an LNP component called PEG. Previous PEG allergies reported reinforce such a hypothesis [29, 30]. Adenoviral vector vaccines have been associated with thrombosis and thrombocytopenia, through a newly characterized

syndrome called VITT, in which anti PF4-antigen antibodies lead to a proinflammatory cascade and platelet activation **(45)**

Several factors play a role in the initiation of these phenomena, with the adenovirus itself, or other vaccine components, such as spike protein and DNA, being associated with thrombosis**.** Myocarditis has also been linked to mRNA vaccines, with both RNA reactogenicity and spike protein binding to ACE2 receptors in the cardiovascular system being the possible culprits. Other important adverse events are of neurological nature. There, a mechanism of molecular mimicry and bystander activation of T cells facilitating an autoimmune response can lead to neuronal dysfunction. Autoimmune responses from the vaccine may also lead to flares of pre-existing autoimmunity diseases or even initiate new onsets in predisposed patients **(46).**

Moreover, biological sex is a factor that seems to correlate with all these responses [32]. PEG allergies, autoimmune phenomena, and thrombosis are more frequent in females. The mRNA vaccines utilize a TLR7 recognition receptor, while viral vector vaccines recruit a TLR9, which activates interferon I responses, a molecule acting as mediator in many autoimmune diseases. Additionally, PEG is a component widely used in cosmetic industry; thus, female individuals are more likely to exhibit past exposure and sensitization to this component. The danger is increased for women receiving oral contraceptives since they already display an increased thrombosis risk. Myocarditis is more frequently reported in young adults, as testosterone enhances Th1 responses and leads to inflammation, while estrogen inhibits them. It is important to note that many females diagnosed with myocarditis are post-menopausal **(46).**

All biological products have adverse effects, calling for heightened pharmacovigilance reflexes .The pharmaceutical industry should focus on improving the current COVID-19 vaccines, as well as future versions, in order to bring about maximization of the therapeutic benefits, while keeping side-effects at bay. The fact that SARS-CoV-2 displays a high mutation rate, thus leading to the emergence of new variants of concern (such as delta and omicron) highlights the necessity of constantly developing new vaccines, in order to successfully confront the new dominant variant. To this end, a third "booster" shot is now required for being protected against the omicron variant, which is currently considered the dominant one **(44)**

Pharmaceutical industries should also take into consideration a wide variety of confounding factors such as genetic predisposition, sex differences, and environmental triggers of the different populations, when designing and developing a vaccine. Novel components can be evaluated for the composition of future vaccines. Theoretically, proven ingredients which are absent from COVID-19 vaccines, but present in other non COVID-19 vaccines (such as latex, egg, or yeast proteins and antibiotics) could be considered for the composition of the final product, at least in non-allergic subjects **(44)**

The genetic background of the patient population should be taken into account, paying attention to polymorphisms leading to susceptibility to different diseases. LNPs, including those utilizing PEG with lower MW, are a future consideration, since these molecules are less immunogenic **(45).** The recombinant adenoviruses as vectors are well used platforms and can be rendered safer by modifying their ability to bind to platelets, or even by using other recombinant viruses as vectors, against which no pre-existing immunity exist in humans, minimizing the likelihood for off-site effects **(45).** Moreover, alternative splicing requires to be taken into consideration, as the introduction of an RNA virus component into a DNA virus may lead to the translation of a different product with unknown effects on the cell **(47).**

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