

## Brief Communication

### Thrombosis with Thrombocytopenia Syndrome (TTS) Associated with COVID-19 Vaccines: Its Safety, Security and Grave Concerns

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#### Abstract:

The COVID-19 pandemic created public health catastrophes around the globe. On December 11, 2020, the first vaccine (Pfizer-BioNTech COVID-19) was introduced for emergency use authorization (EUA). Since then, there have been several COVID-19 vaccines available for the general public. The World Health Organization (WHO) approved more than thirteen COVID-19 vaccines to be used in different parts of the world. The process of approval of a vaccine to be made available on the market requires rigorous quality control (QC) procedures and GCP compliant clinical trials. Due to the unprecedented mortality arising from COVID-19 infections, the vaccines were authorized for emergency use. Hence, some of the vaccines did not pass through rigorous approval process.. Recently, adverse effects from COVID-19 vaccines have been highlighted in studies, with reports ranging from mild to fatal reactions. In February 2024, AstraZeneca announced that its COVID-19 vaccines (Covishield and Vaxzevria), may induce thrombosis with thrombocytopenia syndrome (TTS) in vaccinated individuals. TTS may lead to internal blood clotting that affects various organs of the body. This can trigger complications such as myocardial infarction leading to cardiac arrest, stroke, acute kidney failure and encephalitis. TTS is rarely reported across the globe, and often fall within a three-month period post-administration of the COVID-19 vaccine. Hence, further study is required to identify the exact mechanism that leads to TTS from COVID-19 vaccines.

**Keywords:** COVID-19, vaccine, Thrombosis with Thrombocytopenia Syndrome, TTS, clotting, low platelet count, side effects, cardiac arrest

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#### Introduction

During the public health emergency of international concern (PEIC) due to COVID-19, many vaccines were granted prequalification or authorized for emergency use based on the WHO criteria. As of 2024 14 vaccines with WHO EUL / PQ status have been made available (1). The widely used ones are described briefly below:

Comirnaty by Pfizer-BioNTech is a nucleoside modified mRNA vaccine developed in Germany. This vaccine contains single stranded mRNA sequences that encode the viral S protein. The lipid nanoparticles in which the mRNA is formulated prevent degradation of the mRNA in the host cell (2). Spikevax developed by Moderna Biotech based in Cambridge, Massachusetts; is a mRNA-based vaccine encapsulated in lipid nanoparticles (LNP) works in a similar

fashion (1).

AZD1222 Vaxzevria developed by Oxford-AstraZeneca in the United Kingdom, and Covishield by Serum Institute of India Pvt. Ltd are viral vector vaccines which were previously used. However, these have now been delisted as of 21st March 2024. Vaxzevria is an adenovirus vector-based vaccine which induces expression of S protein in host cells, leading to production of antibodies against the S protein (3).

#### Methods

A detailed literature review was conducted using the search terms "COVID-19", "vaccine", "SARS-CoV-2", "side effects", "Thrombosis with Thrombocytopenia Syndrome", "TTS", "clotting", "low platelet count", "cardiac arrest" and "renal failure". Data bases such as

PubMed, Google Scholar, EMBASE and PMC were employed for this study. The inclusion criteria for this research were: (a) articles in English; (b) original, review and case report articles published between January 2019 to December 2024. The exclusion criterion was articles with insufficient data.

### Discussion

All vaccines should possess the properties of excellent safety and security. This requires several rigorous processes that ensures low risk, effectiveness and safety for the administered individuals. It should also have prompt, continuous, cheap, sustainable and high quality to face the universal immunization requirements. The process of approval of a vaccine to be made available on the market, requires rigorous quality control (QC) procedures and strict clinical trials. Due to the unprecedented mortality arising from COVID-19 infections, the vaccines were authorized for emergency use. Hence, some of the vaccines were not subjected to the long procedures of approval. Recently, side effects from COVID-19 vaccines have been highlighted in studies, with reports ranging from mild to fatal reactions.

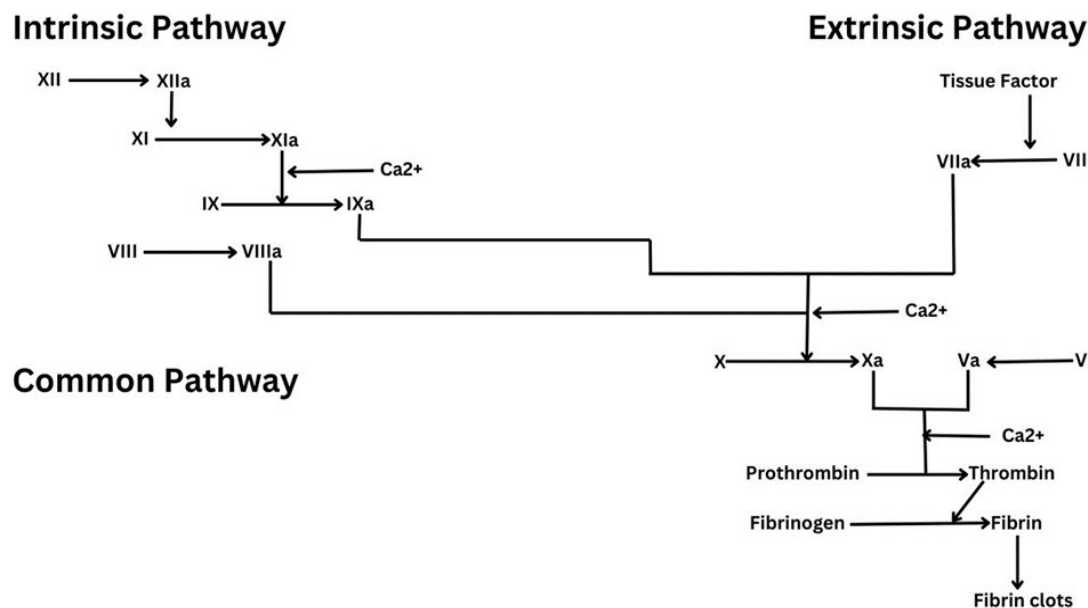
COVID-19 vaccines are observed to have both local adverse effects as well as some systemic reactions. Most commonly, recipients experience pain, erythema, urticaria and swelling at the injection site which usually resolve without treatment (3).

Systemic effects range from mild self-limiting reactions

to more severe and life-threatening reactions. Fatigue, headaches and myalgia were seen among those who received Comirnaty and Spikevax. Other vaccines have led to fever, nausea and fatigue as well. Although rare, severe adverse effects such as severe chest pain, paroxysmal ventricular arrhythmias, hypertension, etc. were reported for Comirnaty. However, the most alarming adverse effects were seen with Vaxzevria, leading to the suspension of its use in March 2021. These include immune thrombotic thrombocytopenia, hemorrhage, anaphylaxis, Guillain-Barré syndrome, bleeding episodes and even death (3). Most common adverse reactions reported were on the nervous system, followed by the gastrointestinal system. Cardiac and vascular complications were less frequent, but more fatal (4).

### Factors associated with internal clotting after COVID-19 vaccination

Several clotting factors like, XII, XI, IX, VIII, VII, prothrombin, fibrinogen etc., are involved in clotting process. There are three pathways associated with the internal clotting mechanism, namely intrinsic, extrinsic and common pathways. After COVID-19 vaccination, the antibodies (IgG/IgM) can bind with the infecting virus and forms an antigen-antibody-complex (AAC). During repeated infection, it can result in cytokine storm and accumulation of several molecules of AAC. The cytokine storm coupled with AAC can trigger and activate the various clotting factors resulting in increased internal clotting (figure.1).



**Figure 1:** Enhanced internal clotting process after COVID-19 vaccination

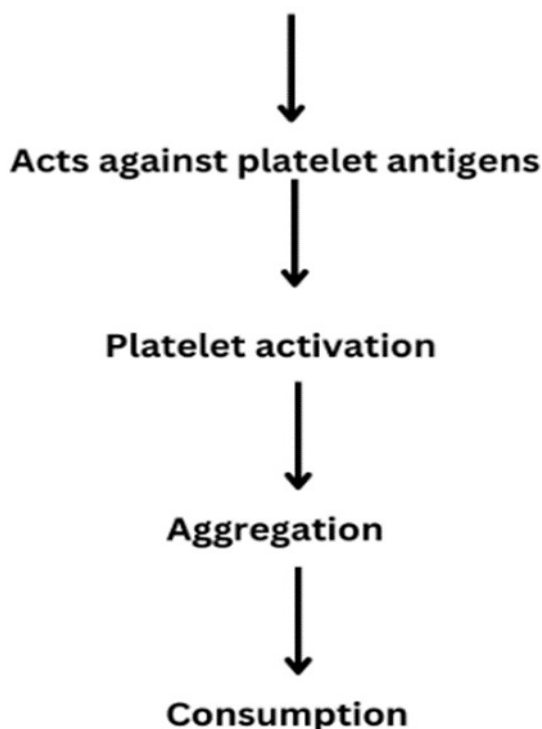
Factors inducing low platelet count after COVID-19 vaccination

Thrombocytopenia, defined as a platelet count less than  $150 \times 10^9/L$  may be caused due to increased platelet destruction, decreased platelet production, increased splenic sequestration, and dilution. Thrombocytopenia related to COVID-19 vaccination is primarily associated with decreased platelet production, as observed in TTS.

#### **Mechanism of thrombosis with thrombocytopenia syndrome (TTS)**

Thrombosis with thrombocytopenia syndrome (TTS), a rare complication observed in patients vaccinated against COVID-19, resembles a more commonly known condition, heparin-induced thrombocytopenia (HIT). Although the exact pathophysiology of TTS is not extensively known, (5) recent reports emphasize the involvement of platelet factor 4 (PF4), a protein implicated in the pathogenesis of HIT (6). This is stored in platelet  $\alpha$ -granules, which play a role in the activation of platelets. In HIT, PF4 is observed to bind with heparin, forming PF4/H complexes, which triggers the development of anti-PF4 antibodies and subsequent platelet activation (6). Unlike in HIT, however, in TTS anti-PF4 antibodies predominantly bind to PF4 alone, rather than the PF4/H complexes (figure 2).

#### **Formation of anti-PF-4 antibodies**



**Figure 2** : Mechanism of Thrombosis with Thrombocytopenia Syndrome (TTS)

#### **Complications of TTS**

TTS is associated with venous thrombotic events, most commonly, within cerebral, splanchnic, and pulmonary vessels. Among the reported cases, the most common complication seen in TTS is cerebral venous sinus thrombosis (7). In a minority of cases, arterial thrombosis is also observed.

#### **Mechanism of myocardial infarction/cardiac arrest after COVID-19 vaccination**

There are several proposed mechanisms of cardiac complications associated with COVID-19. Acute MI is reported more commonly among older patients, which may be associated with underlying comorbidities (figure 3). Along with this, stress arising from COVID-19 vaccination has been proposed as a factor that may play a role in the formation of MI, due to demand ischemia (8). Many studies also report the formation of a prothrombotic state as seen with autoimmune HIT (9). Other studies demonstrate an increased level of immunoglobulin E antibodies, which may suggest allergic vasospasm to be the cause of post-vaccination MI (10).

#### **Mechanism of stroke after COVID-19 vaccination**

The risk of cerebrovascular disease associated with SARS-CoV-2 has been extensively reported, and with further studies, there has been an increased risk of ischemic stroke reported after vaccination. The mechanism for this has been suggested to be hypercoagulability and vascular occlusion observed with TTS (11).

#### **Induction of acute renal failure**

With massive-scale vaccination, various renal diseases with acute renal injury were observed. This included membranous nephropathy, ANCA-associated vasculitis, IgA nephritis, minimal change disease, and renal thrombotic microangiopathy. In one study, the mortality associated with AKI was 2.19 times higher in patients who received COVID-19 vaccination, with coexisting active illness, than those without active illness. Two theories suggested were molecular mimicry of immune response to COVID-19 vaccine, to the natural infection itself, and immunogenicity associated with mRNA vaccines, as AKI was more commonly reported in patients who received mRNA COVID-19 vaccines (12).

#### **Encephalitis after COVID-19 vaccination**

The exact etiology of encephalitis after post-vaccination is not fully understood. However, studies report an increased proinflammatory cytokine expression, which may suggest vaccine-induced autoimmune disease to be a causative factor in the development of encephalitis. Another study suggested potential molecular mimicry between vaccine antigen and self-antigen, or acceleration of an ongoing autoimmune process due to the vaccine (13).

### Psychiatric adverse reactions to COVID-19 vaccination

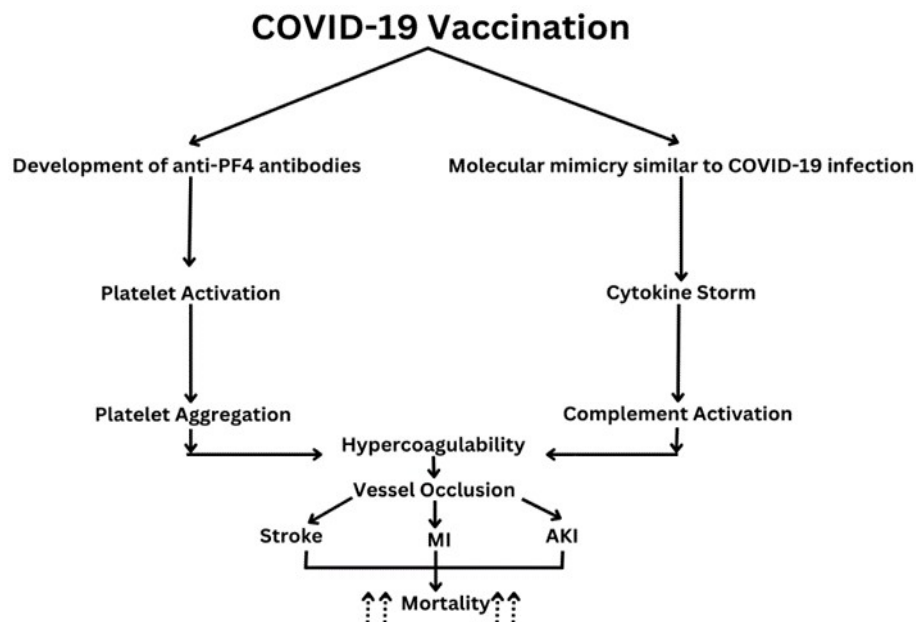
Psychiatric adverse reactions following vaccination have been reported, with Vaxzevria developed by Oxford-AstraZeneca being responsible for a majority of these cases. Altered mental states were common, where patients were disoriented and experienced other symptoms such as labile mood and hallucinations (visual, auditory and tactile). Some patients experienced psychosis, as well as mania and depression. None of these reported patients had previous psychiatric illnesses (14). Although the mechanism of these events are not fully understood yet, some hypotheses state that it may be due to the fact that vaccines will induce similar effects as the disease itself and patients suffering from COVID-19 have shown psychiatric manifestations. Another hypothesis is that these reactions may be precipitations of the stress related to vaccines. Due to misinformation spread about the safety and effects of vaccination, some patients face stress and anxiety about vaccination, which may manifest as psychiatric dysfunctions following vaccination (15).

### Deaths reported after COVID-19 vaccination

Most of the deaths reported following vaccination was in older individuals residing in long-term care facilities. They had multiple different comorbidities, such as hypertension, chronic obstructive pulmonary disease, diabetes, anemia, heart failure, etc. Vaccine-drug or vaccine-disease interactions in these patients may have worsened their underlying conditions, leading to death (16).

However, there have been some cases in which death was due to adverse reactions caused by vaccination. In such cases, the most common causes reported were vaccine-induced immune thrombotic thrombocytopenia (VITT), myocarditis, acute disseminated encephalomyelitis (ADEM), myocardial infarction and rhabdomyolysis (17).

A 22-year-old from Korea who was otherwise healthy, died due to myocarditis following vaccination with Comirnaty. In this case, the myocarditis was said to be possibly related to vaccination (18). A 57-year-old man passed away 2 days after Vaxzeria administration. Upon autopsy, cardiac hypertrophy, myocardial scars, coronary sclerosis, and a fresh myocardial infarction was found (17). An 85-year-old woman with a history of rheumatoid arthritis, hyperlipidemia, and asthma and a cerebrovascular accident developed rhabdomyolysis following vaccination, and passed away from complications of the disease (19-21). There are a few cases from the deaths that have been reported following vaccination for COVID-19 (22, 23). While it may be alarming, a causal relationship has not been established in many of these cases. Since the introduction of these vaccines, deaths due to COVID-19 have significantly reduced as well. Cytokine storm formed during the SARS-CoV-2 infection has resulted in the increased severity of COVID-19 disease (24).



**Figure 3 :** Pathogenesis of TTS and other complications after COVID-19 vaccination

## Conclusions

There are more than thirteen different types of COVID-19 vaccines available for human use. These vaccines should undergo strict quality control and GCP compliant clinical trials before its application in the human population. But during the COVID-19 pandemic, considering its spread and mortality rate, the WHO approved and recommended for emergency use authorization (EUA). Recently, AstraZeneca admitted that its COVID-19 vaccines (Covishield and Vaxzevria) can cause a fatal side effect called TTS. Many of these COVID-19 vaccines elicited severe vaccine reactions in the body. It includes internal clotting, low platelet count resulting in deaths due to myocardial infarction/cardiac arrest, stroke, and acute renal failure. Many of the vaccinated individuals have also exhibited varying degrees of psychiatric disorders. Further study is required to link the association between COVID-19 vaccination with its potential adverse effects.

## Conflict of interest

The authors declare that there is no conflict of interest.

## Ethical clearance

Not required.

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None received.

## Data Availability

The research data associated with the paper is available.

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