



## An Update on Thrombotic Thrombocytopenia Syndrome Induced by a COVID-19 Vaccine from an Indian Perspective

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### Abstract

Based The Oxford-Astra's Covid vaccine is sold as Covishield™ in India, which is manufactured and marketed by the Serum Institute of India. In India, 175 crore doses of the same vaccine produced by the Pune-based Serum Institute, have been given out in India. The parent company has recently made a startling disclosure about probable serious adverse effect of the vaccine that it can cause thrombosis with thrombocytopenia syndrome (TTS). Naturally, this opens a Pandora's Box about the safety and adversity of the injection that each of us received. In few cases some adverse effects have been reported including few recorded deaths. Social media users are debating the vaccine's safety in response to this admission. While worries are legitimate, it's important to separate facts from myths. Vaccines can cause some common side effects and, in some instances, very rare serious side effects but the benefits always outweigh the risks. India could beat the pandemic due to timely administration of the vaccine.

**Keywords:** SARS-CoV-2; Vaccine; Covishield; Side effects; Thrombosis with thrombocytopenia syndrome; Safety; Benefit.

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## 1. Introduction

Vaccines have demonstrated their enormous public health value in lowering morbidity and death linked to transmissible diseases and have been essential in the fight against infectious diseases. World-wide almost six million deaths/year are prevented and 368 million life/years as well as 96 million disability-adjusted life/years saved by vaccines [1].

Indian Government launched a massive vaccination drive against COVID-19 on 16 January 2021. India with its estimated population of 1380 million (as of 2020) planned to administer the vaccine to all its citizens [2], where importing the vaccines from abroad was not feasible for India due to its large population. The Government of India initially procured 600 million doses of the COVID-19 vaccine from the manufacturers, targeting 300 million beneficiaries which included frontline and health workers along with elderly population above 50 years [4]. Covishield, produced by Serum Institute of India and Covaxin produced by Bharat Biotech Ltd were procured by the government, and were administered initially as both were approved by CDSCO, India's drug regulator for restricted emergency use [3].

AstraZeneca is a British-Swedish pharmaceutical company that developed the COVID-19 vaccine in collaboration with the Oxford University [5-7]. AstraZeneca has partnered with SII to supply vaccine only to the Indian Government but also to various low and middle-income countries. Covishield is the brand name for the AstraZeneca COVID-19 vaccine that is manufactured and marketed by SII, one of the commonest vaccines in use by the Indian population.

Covishield had demonstrated considerable efficacy (72-85%) against infection, 92% protection against hospitalization with delta variant and 86% protection against hospitalization with alfa variant. The Clinical Trials did not report any severe allergic reaction but TTS was reported 3-30 days following vaccination [8]. Same vaccine at times can produce different responses in the receivers because of myriad variables associated with process in vaccination. These variables can include variability in individuals' immune response, age, hormonal differences etc. In rarest cases, body might generate antibodies against its own platelets leading to abnormal clotting which is known as Thrombosis with Thrombocytopenia Syndrome

(TTS) [9,10]. According to more recent data, the Indian government's committee on Adverse Events Following Immunization (AEFI) said at least 36 cases of TTS have been vetted and confirmed to have been caused due to Covishield [11]. The committee's last report, which was made public in June last year, showed that of these cases 18 deaths were reported. Almost all of these TTS cases pertain to 2021, which was the first year of Covid-19 vaccination in the country [12]. In this review we have focused on the current status of Covishield vaccine and its moderate to severe adverse effects in Indian population as well as their awareness regarding the risk to benefit.

## 2. Covishield

Covishield vaccine is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Following administration, the genetic material of part of corona virus is expressed which stimulates an immune response [13]. This Vaccine has been approved for active immunization of individuals aged 18 years and older for the prevention of coronavirus disease 2019 (COVID-19). It consists of two doses of 0.5 ml each. The Indian government has recommended that the time interval between the 1<sup>st</sup> and 2<sup>nd</sup> dose (Table 1) should be between 12-16 weeks [14]. The possible side effects of Covishield Vaccine include reactions at the site of injection (such as pain, swelling, and redness), headache, nausea, vomiting, muscle pain, joint pain, fatigue, malaise (general discomfort), fever, chills, and flu-like symptoms. Most of these side effects are mild and temporary (subside within 2-3 days) that subside on their own [15].

Covishield Vaccine (Figure 1) contains a non-replicating virus (a weakened chimpanzee adenovirus that causes common cold), that is genetically engineered to produce coronavirus proteins in the body, but the virus is weakened and cannot cause the disease. It provides active immunization against Covid-19 infection that helps you fight the virus if exposed. This means there is a reduced risk of developing the illness and its consequences [16].

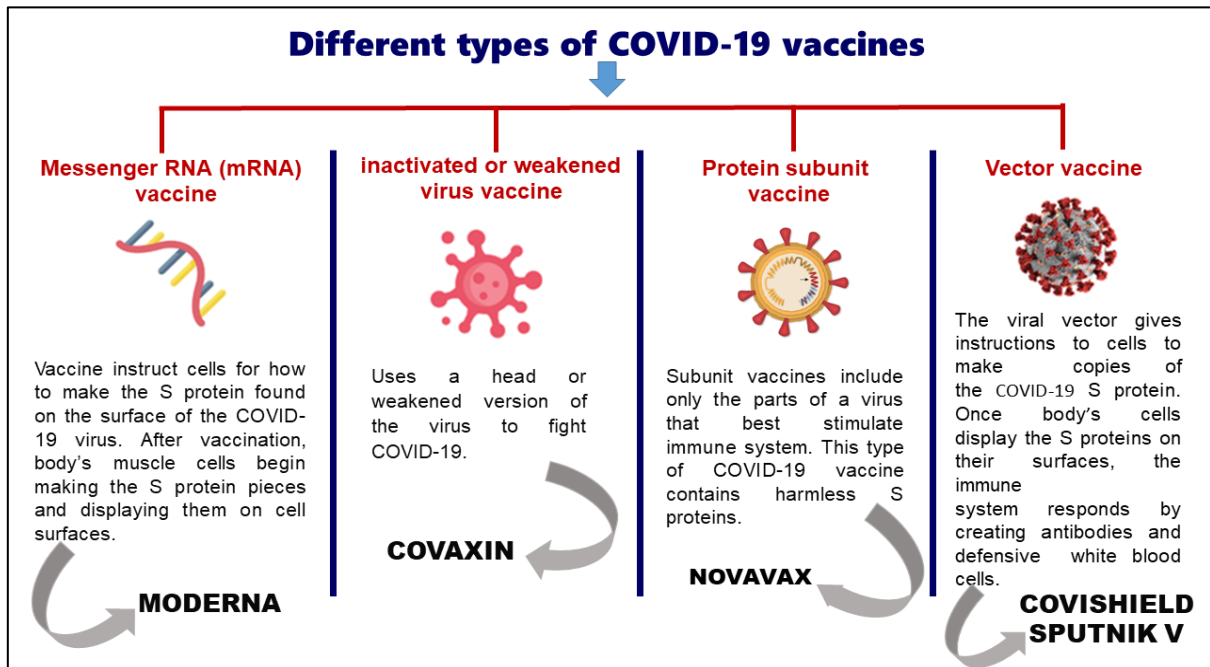


**Table 1:** Overview of Covishield

Developer	Developed by the University of Oxford in collaboration with Swedish-British drug maker AstraZeneca
Commercial manufacturer	Serum Institute of India (SII) is the manufacturing partner in India
Constituents	Contains the genetic material of the SARS-CoV-2 spike protein
Action	The body's immune system is supposed to recognise this protein as a threat, and work on building antibodies against it.
Dose	Covishield Vaccine is a 2-dose (0.5ml) vaccination regimen. The second dose is administered between 4 to 6 weeks after the first dose.
Vaccinated with Covishield in India	1,74.94.17,978

Source:

**Figure 1:** Types of COVID-19 vaccines.



Source: <https://projectsanchar.org/faqs-vaccine/>

### 3. Excipients in Covishield™

One dose (0.5 ml) contains (Table 2): COVID-19 Vaccine (ChAdOx1-S\* recombinant)  $5 \times 10^{10}$  viral particles (vp) [17].

\*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS CoV 2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells.

COVISHIELD™ contains the following excipients:



**Table 2:** Excipients of Covishield.

Sl. No.	Excipients
1	L-Histidine
2	L-Histidine hydrochloride monohydrate
3	Magnesium Chloride Hexahydrate
4	Polysorbate 80
5	Ethanol
6	Sucrose
7	Sodium chloride
8	Disodium edetate dehydrate
9	Water for injection

Source:

### 3.1 Common adverse reactions

With the COVISHIELD™ vaccination, the following adverse reactions and side effects have been documented [18].

1. Extremely prevalent (may impact over 10% of individuals) - soreness, warmth, pain, or itching where the injection was

administered; overall sense of illness; weariness; chills or a fever; headache; feeling nauseous (nausea); joint pain or muscle ache (Table 3).

2. Common (potentially affecting over 10% of the population) Fever, sore throat, runny nose, cough, chills, pain in the arms or legs, fever, nausea, vomiting, or diarrhea, swelling or redness where the injection was administered.
3. Seldom occurring (may impact as many as 1 in 100 persons) symptoms include fatigue or light-headedness, abdominal discomfort, swollen lymph nodes, profuse perspiration, itchy skin, rash, or hives.
4. Unknown (the frequency cannot be ascertained from the information provided) -severe swelling of the lips, tongue, or throat (which may make it difficult to breathe or swallow), severe allergic reaction (anaphylaxis).
5. Rest: Very rarely (less than 1 in 100,000 vaccinated individuals) has major blood clotting (venous and/or arterial thrombosis) and low platelet count (thrombocytopenia) been reported together.

**Table 3:** Possible side effects of Covid-19 vaccine

Sl. No.	Common side effects	Common side effects reported after the second dose	Long-term side effects
1	Redness, pain or swelling at the site of injection	Extreme fatigue	Persistent fever with chills
2	Body and muscle pain	Painful arm	Acute muscle pain
3	Dizziness	Fever with chills	Thromboembolism
4	Malaise, feeling ill, uneasy or discomfort	Headache	Deep vein thrombosis (DVT)
5	Fatigue, feeling tired	Diarrhoea	Severe allergic reactions such as anaphylaxis
6	Headache	Nausea and Vomiting	-
7	Fever	-	-
8	Chills	-	-
9	Nausea	-	-
10	Diarrhea	-	-

Source: Authors.

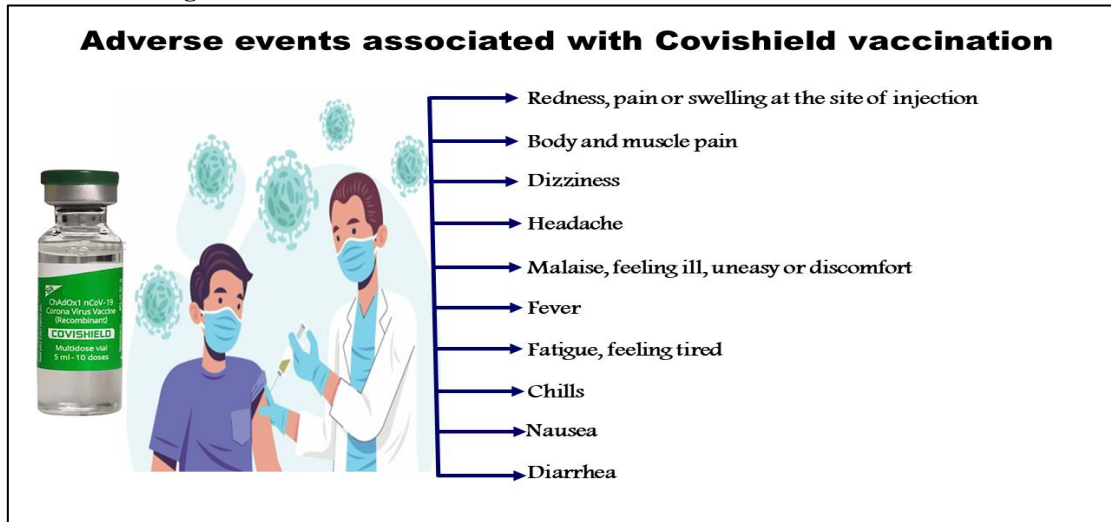


### 3.2 Vaccines and Serious Adverse Events

The majority of COVID-19 vaccinations have been associated with adverse events, most of which are moderate (injection site discomfort, myalgia, headaches, weariness, and tiredness) and go away in a few days. In teenagers aged 12 to 15, injection site pain accounted for more than 90% of adverse responses, followed by headache and fatigue (>70%), myalgia and chills (>40%), arthralgia and pyrexia (>20%). These are the data that are posted and updated on a regular basis on the central adverse drug reaction (Figure 2)

reporting platforms run by the UK government [19]. Yet, a small percentage of individuals developed uncommon adverse effects, some of which were lethal. The early use of vaccine was linked to several reports of anaphylactic reactions and safety concerns, which led to recommendations for closer patient monitoring following injection and even for avoiding vaccine in individuals with a history of allergic reactions. The rates of major adverse events were significantly decreased by these methods [20, 21].

Figure 2: Common adverse effects associated with Covishield vaccination.



Source: <https://www.pacehospital.com/possible-covid-19-vaccine-side-effects-and-its-duration>

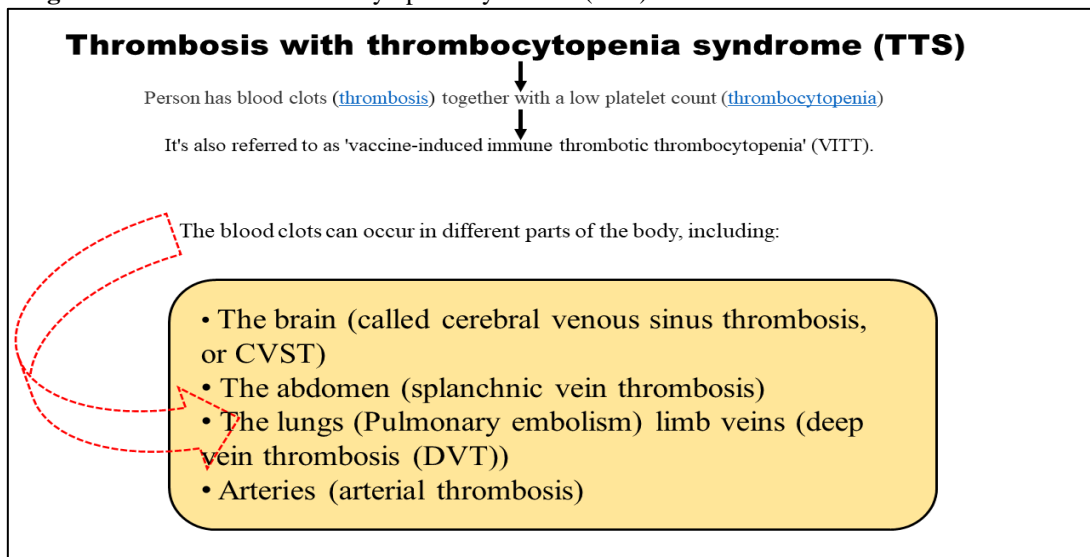
### 3.4 Thrombosis-thrombocytopenia syndrome (TTS)

Thrombosis-thrombocytopenia syndrome (TTS) is a rare but serious condition characterized by decreased platelet counts (thrombocytopenia) and embolism formation (thrombosis). In addition to neurological deficits, TTS (Figure 3) typically manifests as severe migraines, stomach discomfort, leg edema, and dyspnea [22]. A medical diagnosis consists of imaging studies to detect embolism and blood tests to measure platelet counts [23]. Treatment for TTS involves a

multidisciplinary approach that includes supportive care, anticoagulant medication to prevent further clotting, and hospitalization. Plasmid exchange and intravenous immunoglobulin (IVIG) may also be utilized to control immune-mediated reactions and preserve platelet counts [24].



**Figure 3:** Thrombosis-thrombocytopenia syndrome (TTS) associated with Covishield vaccination.



Source: <https://www.healthdirect.gov.au/thrombosis-with-thrombocytopenia-syndrome-tts>

**Table 4:** Tiers classification of TTS.

Tier 1	Tier 2
Uncommon site of thrombosis (eg. brain – cerebral venous sinus thrombosis [CVST] or gut – eg. splanchnic vein, associated with bowel ischaemia and surgery, portal vein or other rare venous and arterial thromboses)	Common sites of thrombosis such as leg or lungs (eg. venous thromboembolism, deep vein thrombosis, pulmonary embolism).
May also concurrently have thrombosis in more common locations (eg. deep vein thrombosis or pulmonary embolism)	Platelet count < 150,000 per microliter.
Platelet count < 150,000 per microliter.	Positive anti-PF4 ELISA result is required.
Positive (+) anti-PF4 ELISA result is supportive, but not required for diagnosis.	

Source: Authors.

Healthcare professionals closely monitor patients with TTS due to the potential for catastrophic complications, such as organ damage and even death. For those affected by this uncommon but serious illness, prompt identification and monitoring are important to improving outcomes [25]. According to the World Health Organization's (WHO) records from 2023, TTS emerged as a novel adverse event (Table 4) associated with immunization in individuals receiving COVID-19 non-replicant viral vector-based injections [26].

Tier 1 tends to be associated with more severe presentations and carries a higher risk of morbidity and mortality than Tier 2. Evidence

suggests that Tier 1 is more common in younger age groups.

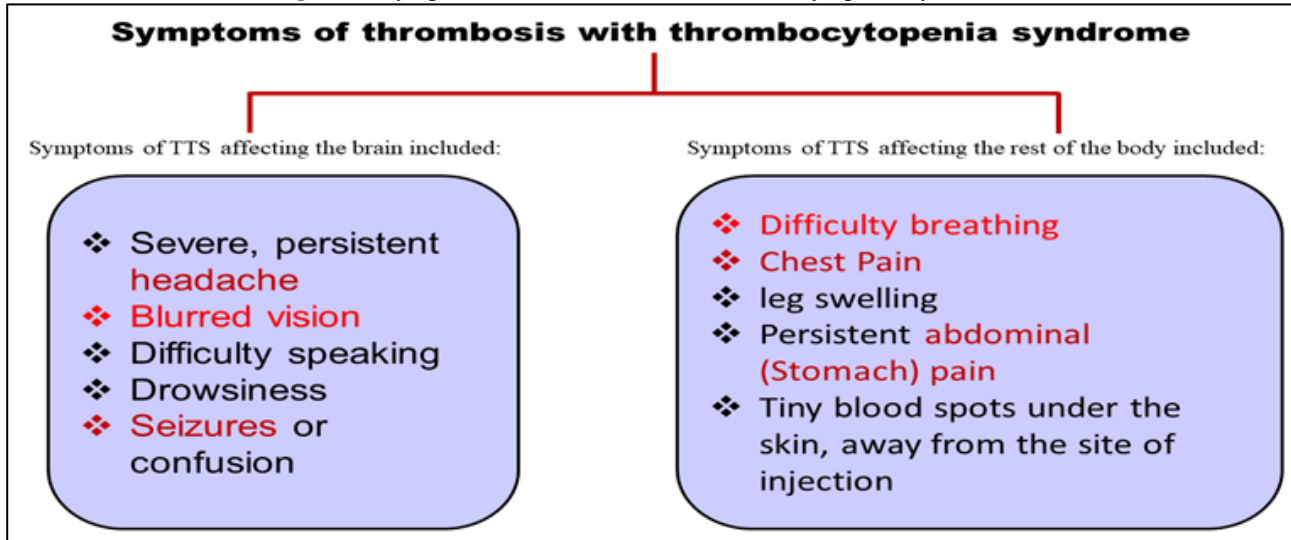
### 3.5 Clinical characterization of TTS

Fifty to fifty percent of people infected with SARS-2-CoV-2 show no symptoms [27], fourteen percent get seriously ill, and five percent are severely ill [28]. Particularly in the elderly or those with co-morbidities such as diabetes mellitus, renal disease, and cardiovascular conditions, the clinical course of COVID-19 can be severe and occasionally linked to complications such as venous thromboembolism (Figure 4) events (VTEs), acute respiratory distress syndrome, severe inflammatory response syndrome, and



multi-organ dysfunction syndromes [29]. More over 25% of COVID-19 patients get VTEs [30].

**Figure 4:** Symptoms of thrombosis with thrombocytopenia syndrome.



Source: <https://www.nature.com/articles/s41541-022-00569-8>

Uncertainty surrounds the pathogenesis of COVID-19 related thrombosis. COVID-19 causes an accompanying hyper-inflammatory response that is intricately linked to various pathways, including coagulopathies such disseminated intravascular coagulation (DIC), endothelial injury, direct invasion of cells like type 2 pneumocytes, and pro-inflammatory mediators [31].

In order to support their function in immunomodulation and hemostasis, platelets include co-stimulatory molecules, chemokines, chemotactic factors, and different adhesion molecules in their membranes and granules. Through the expression of Toll-like receptors (TLRs), which release inflammatory cytokines, platelets cause blood coagulation, inflammation, and adaptive immune responses. They also activate T cells by expressing major histocompatibility complex (MHC) and key costimulatory molecules. Large volumes of extracellular vesicles are released by platelets, and these vesicles can interact with a variety of immunological mediators. As a result, platelets serve purposes other than aggregation, and their interactions with immunological response, inflammation, and haemostasis enhance the body's defense systems [32].

Nearly one in three COVID-19 infected inpatients (31.6%) and those with severe COVID-19 (57.7%) experienced thrombocytopenia [33]. Most patients had mild thrombocytopenia when they first arrived, but in certain cases, severe thrombocytopenia necessitated careful consideration of both bleeding and thrombotic risk. In such circumstances, thrombocytopenia has been linked to a number of pathophysiological causes. These include bone marrow suppression that is somewhat like to that seen in sepsis; megakaryocytic and hemopoietic precursor cell function and synthesis are probably affected by direct SARS-2-CoV-2 infection of the marrow.

#### 4. How Does Covishield Operate?

The AstraZeneca vaccine which utilizes a chimpanzee DNA adenovirus elicits an immune response only to the viral healthy protein incorporated into the host DNA, not to the adenovirus itself. The genetic material of the spike protein of SARS-CoV-2 is combined with a weaker version of the adenovirus, a common cold virus that infects chimpanzees. The viral vector aids in the body's immune response development. It aids in the production of antibodies by immune cells against the antigen, preparing the cells for the next viral attack. It should be mentioned that



the Covishield vaccination serves as a preventative measure rather than a cure for the infection [34].

#### 4.1 Post COVID-19 Syndrome and Risk of Thrombosis

There is growing scientific and clinical data regarding the long-term and subacute effects of COVID-19, which can impact several organ systems [35]. According to early studies, the SARS-CoV-2 infection may still cause symptoms such as arthralgia, fatigue, dyspnoea, chest pain, cognitive impairment, and a reduction in quality of life [36]. These consequences could be caused by cellular damage, a strong innate immune response that produces inflammatory cytokines, and a procoagulant condition brought on by an infection with SARS-CoV-2 [37].

It is unknown what will happen to patients with COVID-19 and VTE in the long run. High rates of mortality (24%) and significant bleeding (11%), within the first 30 days after COVID-19-associated VTE, were described in recent prospective research evaluating long-term haemorrhage, recurrence, and death. A poor prognosis was predicted by thrombocytopenia, malignancy, and ICU admission [38, 39].

#### 4.2 Significant observation for Indian users of Covishield

In 2021, the year of the country's first Covid-19 vaccine, the Government Board on Adverse Events Following Immunization (AEFI) verified 18 fatalities from TTS and assessed at least 36 TTS cases [40]. However, legal barriers like permissions from multiple regulatory bodies and the product being manufactured by an Indian company that complies with Indian laws and territory mean that affected Indian individuals are unlikely to be able to register with the British application.

#### 4.3 Do not panic

According to experts, TTS was unusual in India but was recorded earlier in the pandemic by European countries. During the vaccination effort, an old ministry authority on health and wellness stated, "TTS is an unusual negative effect, rarer still in Indians and also South Asians compared to Europeans." However, there is enough evidence to show that vaccinations save lives—the benefits

outweigh the risks. Furthermore, the risk is not only uncommon but also very significant within the first few weeks following the initial injection. Many Indians have now received three bullets, and considering that, a very long period has passed. In addition, the strategy presented for Covishield consistently contained a warning about the peculiar issue. "During post-authorization usage, an extremely uncommon and severe set of adverse effects has been observed." Examples have included patients with autoimmune disorders and those with a history of thrombosis. It is important to consider both the benefits and risks of immunization for these individuals [41].

#### 4.4 Current situation

Many individuals in India do not currently feel the need for vaccinations. Despite the fact that the illness has spread, Indians now have high antibody levels. Vaccinations are not necessary unless a person has a severely impaired immune system [42]. He adds, "And even after that, they should get the more recent shots that can protect against later COVID-19 versions like Omicron." For younger girls who were at a lower risk of severe illness at the time he included, an example might be made using other injections.

#### 4.5 Current Management Recommendations

According to the most recent updated recommendations from the American Society of Haematology and the Expert Haematology Panel (UK), patients who exhibit thrombosis symptoms 4–30 days after receiving the Janssen COVID-19 vaccination or the Vaxzevria vaccine should be carefully evaluated [43].

The four diagnostic criteria below must be met:

1. Receipt of a COVID vaccine (Janssen/Vaxzevria) 4 to 30 days previously;
2. Thrombosis (often cerebral or abdominal);
3. Thrombocytopenia;
4. Positive PF4-HIT test using ELISA.

Even though this thrombotic complication is still extremely uncommon, getting COVID-19 still carries a significant risk of death and other serious consequences, such as thrombosis. Regulators in





the UK and the US currently advise seeking an urgent medical evaluation for TTS if any of the following symptoms appear four to thirty days after vaccination: severe headache, altered vision, abdominal pain, nausea, vomiting, backache, dyspnea, swelling in the legs, petechiae, or easily bruised [44].

A complete blood count with a platelet count and peripheral blood smear, imaging for thrombosis based on signs and symptoms, PF4-ELISA (HIT assay) using blood collected before any therapies, and fibrinogen level should all be scheduled immediately if TTS is suspected [45].

## 6. Vaccine awareness

It is anticipated that more than 70% of Indian population who were vaccinated against COVID-19, received Covishield. Ever since the it has been acknowledged publicly by AstraZeneca regarding possible link of TTS with the vaccine, the common man are calling doctors and physicians to know how to protect themselves against a probable heart attack, which is a SOS call only [46]. Additionally, some people who have lost their loved ones after receiving the immunization are linking Covishield to their death and maybe planning to sue the company in court.

Citizens who have lost a loved one as a result of a vaccines significant side effects become extremely nostalgic and occasionally enraged [47]. Physicians report that side effects are common with most DNA vaccinations, and that in rare cases, these side effects might result in TTS, which is characterized by low platelet counts (thrombocytopenia) and blood clots (thrombosis), both of which are essential for blood clotting. These clots frequently move to the brain/heart, where they can cause a stroke/ heart attacks [48]. But according to medical professionals and epidemiologists, the chance of developing TTS is barely seven to eight per million vaccine recipients.

Physicians feel that there are considerably more advantages of Covid-19 vaccinations than disadvantages. Even though one in 100,000 people may not have benefitted from the vaccine, Covid-19 was the second leading cause of mortality worldwide in 2021. Covid-19 and a poor lifestyle both raise the danger, which can occasionally turn deadly and claim lives. Patients with comorbidities also have a significant risk of

adverse consequences, which can occasionally be fatal. For this reason, if someone feels unwell after receiving a vaccination, they should see a doctor immediately or get admitted to the hospital. Early detection of vaccine-related adverse effects prevents deaths and brings the situation under control [49].

## 7. Conclusions

According to recent research on AstraZeneca and the Covishield vaccine, the company has admitted in court documents that the vaccine may cause Thrombosis with Thrombocytopenia Syndrome (TTS), a rare adverse event that includes embolism and a decrease in platelet count. Despite these findings, medical specialists emphasize that although TTS is a serious issue, the benefits of the COVID-19 vaccination—which includes Covishield—rarely outweigh the risks.

The World Health Organization (WHO) has issued guidelines to help medical professionals manage potential scenarios and to increase awareness of TTS in relation to the COVID-19 immunization. Although there is a strong suggestion for the uncommon side effects, the safety, security, and efficacy of the Covishield vaccine, along with other COVID-19 immunizations, are nevertheless supported by a substantial amount of professional test data and real-world evidence. Authorities in charge of regulations emphasize the importance of immunization in preventing severe COVID-19 outcomes. When a patient exhibits TTS symptoms, it is advisable to diagnose them quickly and start treating them right once. In order for a more comprehensive picture of risk factors and susceptible groups to emerge, it is crucial to report confirmed and suspected instances to regulatory organizations.

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## Conflict of Interest

We declare that we have no conflict of interest.

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