Research Article

Approved Covid-19 Vaccines and their Adverse Effects: A Narrative Review

Moyosore Olatunde Olajuwon1, Ikechukwu Okereke2, Sakshi Mishra3*, Wajeeha Khalid4, Sheheryar Sharif5, Asma Nasir6, Alaa Irshad7, Ugochi Ojinnaka8, Aliza Bukhari9, Oluwasegun Shoewu10, Sadaf Munir6, Jasmine Kaur Sandhu11, Antonia Lisseth Valle Villatoro12, Belonwu Valentine Okafor13, Wilson Olaotan Vaughan14

1Washington University of Health and Sciences, Belize, USA
2University of Nigeria Faculty of Medicine, Nsukka, Nigeria
3Bangalore Medical College and Research Institute, Bangalore, India
4Karachi Medical and Dental College, Karachi, Pakistan
5Frontier Medical and Dental College, Pakhtunkhwa, Pakistan
6Dow University of Health Sciences, Karachi, Pakistan
7Allama Iqbal Medical College, Lahore, Pakistan
8Xavier University School of Medicine, Oranjestad, Aruba
9University College of Medicine and Dentistry, Lahore, Pakistan
10Obafemi Awolowo College of Health Sciences, Ife, Nigeria
11Sri Guru Ram Das Institute of Medical Sciences and Research, Punjab, India
12Universidad de El Salvador, San Salvador, El Salvador
13Nnamdi Azikiwe University College of Health Sciences, Awka, Nigeria
14Kharkiv National Medical University, Kharkivs'ka oblast, Ukraine

*Corresponding author: Sakshi Mishra, Department of Internal Medicine, Bangalore Medical College and Research Institute, India

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Abstract
COVID-19 has evolved into a global pandemic, affecting millions. An effective vaccine is the need of the hour to curb this pandemic, playing a role in increasing herd immunity, preventing severe disease, and reducing the ongoing health crisis. According to the WHO (World Health Organization) draft landscape of COVID-19 vaccines, around 64 vaccine candidates are in clinical assessment. So far, WHO has approved five vaccines; Pfizer, AstraZeneca, Johnson & Johnson, Moderna, and Sinopharm. Although vaccine technology is proposed to be safe, the adverse effects of the vaccines are not yet fully characterized. Given the importance of the vaccine in fighting this public health crisis, understanding the adverse effects of the approved COVID-19 vaccines is crucial.

This review summarizes the current state of knowledge regarding adverse events of the COVID-19 vaccines. These adverse events may include; PE (pulmonary embolism), DVT (Deep venous thrombosis), allergic reactions, CVST (cerebral venous sinus thrombosis), and GBS (Guillain-Barre Syndrome). These findings should be interpreted in light of the proven beneficial effects of the vaccine, and awareness should be spread regarding these adverse effects so that patients can seek early care.

Keywords: Covid-19 Vaccine

1. Introduction
COVID-19 has evolved into a global pandemic affecting the healthcare system all around the world [1]. It has led to more than 157 million confirmed cases and more than 3 million deaths until now [2]. It has not only affected the mental health of the general public but has also adversely affected the mental health of physicians involved in the care of these patients. Several studies have revealed a significantly elevated prevalence of depression, anxiety, insomnia, and emotional distress among health care workers [3]. Despite the global spread of the virus, a large percentage of the people have escaped infection and remained non-immune to SARS-CoV-2. Vaccination can play an important role in increasing population immunity, preventing severe disease, and reducing the ongoing health crisis. It seems to be the only solution to curb this ongoing pandemic. Rapid global efforts to develop and test vaccines against SARS-CoV-2 have led to an unprecedented number of candidate vaccines starting clinical trials during 2020 [4]. There are a few licensed vaccines against COVID-19, and efforts are being made to generate safe and efficacious vaccines for COVID-19 prevention.

According to the WHO draft landscape of COVID-19 candidate vaccines, around 64 vaccine candidates are in clinical assessment. The phase 3 vaccine candidates include a variety of vaccine: vector vaccines (AstraZeneca, CanSino, and Janssen), mRNA-based vaccines (Moderna and Pfizer), inactivated vaccines (SinoVac/Sinopharm, and Bharat Biotech), and adjuvanted recombinant protein nanoparticles (Novavax) [5]. So far, WHO (World Health Organization) has approved five vaccines; Pfizer, AstraZeneca, Johnson & Johnson, Moderna, and Sinopharm. Although this novel vaccine technology is proposed to be safe, the adverse effects of the vaccines are not yet fully characterized. Given the importance of the vaccine in fighting this public health crisis, understanding the adverse effects of the approved COVID-19 vaccines is crucial.
According to a study, immediate allergic reactions such as anaphylaxis can occur at a rate of 11.1 per million doses of the Pfizer COVID-19 vaccine. Anaphylaxis has also been demonstrated with the Moderna COVID-19 vaccine [6]. Currently, the specific mechanism of adverse effects and the inciting antigen have not been identified. In this review, we describe the adverse effects of vaccines as reported so far in the literature. Several case reports, case series, and a cohort study are included in our review. We provide a summary of the age of the participants, symptoms onset, outcomes, and type of adverse reaction as elicited by each vaccine. We also elaborate on a cohort study done to assess the side effect profile of Oxford-AstraZeneca.

2. Methods and Results
To identify articles discussing adverse effects associated with COVID-19 vaccination, a review of the PubMed database was conducted using the search terms "COVID-19 Vaccines"[Mesh] AND "adverse effects" [Subheading]. Filters for human studies, case reports, Adults: 19+ years and articles written in the English language were applied. The total number of articles retrieved was 18. These records were then screened by title and abstract content. A total of 11 articles were included in our review. The total number of patients in our study was 65.

3. Discussion
Coronavirus is being considered the respiratory virus but other presentations are also possible, and some are frequently emerging [7]. Since the end of 2020, many vaccines have been approved for use as a prophylactic measure against COVID-19 infection. Even though preliminary data have suggested these vaccines to be generally safe, adverse effects have been reported in several cases. We provide an overview of all the adverse events reported so far, to aid the clinicians in picking up any such adverse reaction in the future. Until now, WHO has approved Pfizer, AstraZeneca, Moderna, Johnson & Johnson, and Sinopharm. Pfizer and Moderna vaccines were granted emergency approval in December 2020. Both vaccines utilize a novel technology of mRNA encoding the SARS-CoV-2 spike protein enveloped in lipid nanoparticles. These then attach to the cell membrane, gain entry into the cell and start producing spike protein for subsequent antigen presentation and immune system activation [8]. Sinopharm is an inactivated vaccine based on a SARS-CoV-2 isolated from an individual. This vaccine has been licensed in several countries. WHO has granted emergency approval for this vaccine in May. Interim data from phase III efficacy data has shown that Sinopharm has a 99% seroconversion rate of neutralizing antibody and 100% effectiveness in preventing moderate and severe cases of the disease [9]. The AstraZeneca vaccine is based on a modified adenovirus (the vector) expressing the spike protein of SARS-CoV-2, which allows the development of a humoral and cellular immune response against the virus [10].

Our Dataset had 65 patients. Most of these adverse effects were with Pfizer, Moderna, AstraZeneca, and Sinopharm. The majority of these adverse reactions occurred with 1st dose of the vaccine. The age group of our dataset ranged from a 22-year-old man to a 66-year-old woman. Demographic details of the study are mentioned in Table 1. The side effect profile of these vaccinations can be said to be diverse. Side effects range from allergic reactions like anaphylaxis to thromboembolic phenomena like CVST (Cerebral venous sinus thrombosis) and DVT (Deep venous thrombosis). So far, 31 cases of anaphylaxis, 22 of thrombocytopenia, 8 CVST, 1 rash, 1 DVT, 1 multisystem inflammatory syndrome-like illness and, 1 case of GBS have been reported. Allergic reactions to the vaccine are very rare; about 1 individual
in 1 million people will have an allergic reaction to a vaccine. These reactions range from mild symptoms such as hives to severe ones including anaphylaxis. Allergic reactions mostly start quickly (i.e. within 15 minutes) after receiving the vaccine [11]. A total of 31 anaphylaxis cases were reported of which 21 cases were observed in Pfizer while 10 cases with Moderna vaccine. With Pfizer, it happened within 13 minutes [11] while with Moderna, it happened within an average of 7.5 minutes [12]. These anaphylactic reactions were reported with the 1st doses of the vaccines. Another study estimated that immediate allergic reactions such as anaphylaxis can occur at a rate of 11.1 per million doses of the Pfizer COVID-19 vaccine [22].

Currently, the specific mechanisms of allergy and the inciting antigen have not been identified. Around 22 cases of thrombocytopenia were reported. 10 cases were observed with Pfizer while around 12 cases were associated with the Moderna vaccine. Of them, 20 cases were elaborated in a case series [19]. These patients were hospitalized and the majority of them presented with bruising, petechiae, or mucosal bleeding with the onset of symptoms in 5 days (median) post-vaccination. Platelet counts at presentation were at or below $10 \times 10^9/L$ (range $1–36 \times 10^9/L$; median $2 \times 10^9/L$). A total of 8 cases of cerebral venous sinus thrombosis (CVST) were observed with AstraZeneca. Paul-Ehrlich Institute reported the incidence of seven of these CVST cases. They were the first ones to associate sinus vein thrombosis, thrombocytopenia, and bleeding in temporal proximity to COVID-19 vaccine AstraZeneca. Three of these seven patients died. This led to the temporary suspension of the vaccine [23].

Another case of CVST (a 50-year-old man) was reported from the city hospital of Mantua [14]. He had received the first dose of the anti-COVID-19 AstraZeneca vaccine around 11 days back. He had a lack of intra-cerebral blood flow on CT angiography. This led to the diagnosis of brain death, approximately 48 hours after admission to the hospital. The SARS-CoV-2 infection has been associated with hypercoagulability. Physicians should also be alert for signs and symptoms related to thromboembolism when they occur in patients who have recently been vaccinated with the COVID-19 AstraZeneca vaccine [14]. There was also one case of morbilliform rash. It was reported that the rash occurred with both the first and second doses of the vaccine. The rash disappeared within 48 hours [18]. 1 case of Multisystem inflammatory syndrome associated with the SARS-CoV-2 vaccine was also reported [15]. Hypercoagulability is mostly associated with AstraZeneca.

However, a 66-year-old woman with unremarkable medical history developed DVT after the second subcutaneous dose of Pfizer [13]. Guillain-Barre syndrome (GBS) has also been reported with the COVID vaccine [16]. Even though there have been a number of GBS cases post-COVID, but only one case has been reported after the COVID-19 vaccine. The patient was a 37-year-old man who had his first dose of the AstraZeneca 3 weeks back. He presented with a rapidly progressive ascending muscle weakness and back pain in the absence of any other triggers. A diagnosis of Guillain-Barre syndrome was made by correlating the clinical features with cerebrospinal fluid analysis, nerve conduction studies, and MRI of the brain and whole spine [16]. Table 2 summarize vaccine adverse reactions, symptoms onset time period, and outcome of the reaction.
| Reference             | Gender/age                  | Number of individuals (For case series) | Vaccine | Dose  |
|-----------------------|-----------------------------|----------------------------------------|---------|-------|
| Shimabukuro T. [11]   | -                           | 21                                     | Pfizer  | 1st   |
| Shimabukuro T. [12]   | -                           | 10                                     | Moderna | 1st   |
| Carli G et al. [13]   | 66-year-old female          |                                        | Pfizer  | 2nd   |
| Castelli GP et al. [14]| 20–50 years                | 7                                      | AstraZeneca | --   |
| Castelli GP et al. [14]| 50-year-old Caucasian man  | --                                     | AstraZeneca | 1st   |
| Uwaydah AK et al. [15]| 22-year-old man             | --                                     | Sinopharm | 2nd   |
| Patel SU et al. [16]  | 37-year-old man             | --                                     | AstraZeneca | 1st   |
| Carli G et al. [13]   | 66-year-old female          |                                        | Pfizer  | 1st   |
| Castelli GP et al. [14]| 20–50 years                | 7                                      | AstraZeneca | --   |
| Uwaydah AK et al. [15]| 22-year-old healthy man     | --                                     | Pfizer  | 1st   |
| Patel SU et al. [16]  | 37-year-old man             | --                                     | AstraZeneca | 1st   |
| Carli G et al. [13]   | 66-year-old female          |                                        | Pfizer  | 1st   |
| Castelli GP et al. [14]| 20–50 years                | 7                                      | AstraZeneca | --   |
| Uwaydah AK et al. [15]| 22-year-old healthy man     | --                                     | Pfizer  | 1st   |
| Patel SU et al. [16]  | 37-year-old man             | --                                     | AstraZeneca | 1st   |
| Carli G et al. [13]   | 66-year-old female          |                                        | Pfizer  | 1st   |
| Castelli GP et al. [14]| 20–50 years                | 7                                      | AstraZeneca | --   |
| Uwaydah AK et al. [15]| 22-year-old healthy man     | --                                     | Pfizer  | 1st   |

Table 1: Summarizes the demographic details of our dataset.

| Reference             | Vaccine | Dose  | Side effects                  | Symptom onset                | Outcome           |
|-----------------------|---------|-------|-------------------------------|------------------------------|-------------------|
| Shimabukuro T. [11]   | Pfizer  | 1st   | Anaphylaxis                   | 13 minutes (range 2–150 min) | Recovered         |
| Shimabukuro T. [12]   | Moderna | 1st   | Anaphylaxis                   | 7.5 min (range = 1–45 min).  | 8 recovered, remain data unavailable |
| Carli G, et al. [13]  | Pfizer  | 2nd   | DVT                           | 24 h                         | Recovered         |
| Castelli GP, et al. [14]| AstraZeneca | --   | CVST                          | --                           | --                |
| Castelli GP, et al. [14]| AstraZeneca | 1st   | CVST                          | 11 days                      | Braindead after 48hr of hospital admission |
| Uwaydah AK, et al. [15]| Sinopharm | 2nd   | Multisystem inflammatory syndrome-like illness | few hours | Recovered |
| Patel SU, et al. [16] | AstraZeneca | 1st   | GBS                           | 3 weeks                      | Recovered         |
| Tarawneh O, et al. [17]| Pfizer- | 1st   | ITP                           | 3rd day                      | Recovered         |
| Jedlowski PM,         | Pfizer- | 1st and Macular morbilliform | 2 days                       | Recovered         |

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Lee EJ, et al. [18] & 2nd dose & Thrombocytopenia & Onset between 1-23 days (median 5 days) post-vaccination.
Toom S, et al. [20] & Moderna & 1st & Familial thrombocytopenia flare-up & Recovered

Table 2: Elaborates Adverse reactions associated with COVID-19 vaccines.

3.1 Oxford-AstraZeneca and venous thromboembolism
Oxford-AstraZeneca is associated with thromboembolic events. A study was done in Denmark and Norway from 9 February 2021 to 11 March 2021 on patients aged 18-65 years. The vaccinated cohorts comprised 281,264 individuals who received their first dose of AstraZeneca. 59 venous thromboembolic events were observed in the vaccinated individuals. It corresponds to 11 events per 100,000 vaccinations. A higher than expected rate of cerebral venous thrombosis was observed: an excess of 2.5 events per 100,000 vaccinations. The standardized morbidity ratio for any thrombocytopenia/coagulation disorder was 1.52 and for any bleeding was 1.23. Hence, it can be said that the recipients of the AstraZeneca vaccine have increased rates of venous thromboembolic events, including cerebral venous thrombosis. There are also slightly higher rates of thrombocytopenia/coagulation disorders and bleeding, which could be influenced by increased surveillance of vaccine recipients. However, the absolute risks of thromboembolic events are small [24].

4. Conclusion
The SARS-CoV-2 pandemic represents the leading global health emergency, and vaccines are the primary health strategy to eradicate this global challenge. Several vaccination campaigns are being held across all continents to vaccinate people but some adverse effects to vaccination have also been reported. The SARS-CoV-2 infection has been associated with hypercoagulability, with a high incidence of venous thromboembolism including PE (pulmonary embolism) and DVT (Deep venous thrombosis). Similarly, when we inject some form of SARS-CoV-2, they may produce similar conditions and produce a hypercoagulable state. Physicians should also be alert for signs and symptoms related to thromboembolism when they occur in patients who have recently been vaccinated with the COVID-19 AstraZeneca vaccine. Other adverse effects included allergic reactions, CVST, GBS, and rash among others. These findings should be interpreted in light of the proven beneficial effects of the vaccine, and awareness should be spread regarding these adverse effects so that patients can seek early care.

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