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Serious complications of COVID-19 vaccines: A mini-review

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ABSTRACT

The most promising approach of fighting COVID-19 and restraining the course of this pandemic is indisputably the universal vaccination of the population with safe and effective vaccines. However, besides the common and usually mild side effects of the authorized vaccines, some rare, major adverse reactions are increasingly being reported worldwide during the post marketing surveillance phase of vaccines' circulation, such as anaphylaxis, vaccine-induced thrombotic thrombocytopenia, myopericarditis and Guillain-Barré syndrome. Despite rare cases with complications from COVID-19 vaccines, the net benefit-risk ratio shows a clearly favorable balance towards COVID-19 vaccination for all age and sex groups. Vaccine adverse events should be identified early and monitored closely. As many aspects of these adverse effects remain still obscure for the medical community and the relevant stakeholders, it is also highly important to be promptly reported. Nonetheless, these complications should not constitute a reason to change the vaccine policy and further studies are needed to alleviate concerns and reluctance to COVID-19 vaccinations.

Since its first occurrence in December 2019, the novel coronavirus disease 2019 (COVID-19) pandemic has caused millions of deaths around the globe and, unfortunately, continues to challenge even the most resilient healthcare systems. Besides infection control measures, the most promising approach of winning the battle against the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) and restraining the course of this pandemic is indisputably the universal vaccination of the population with safe and effective vaccines [1].

Several vaccines using distinctive technologies and platforms are in the pipeline and some of them have already been approved or granted emergency use authorization (EUA) and are administered in multiple countries globally. The first approved vaccine by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) was the vaccine developed by the Pfizer and the BioNTech [2,3]. Currently, there are two main types of available COVID-19 vaccines: the messenger RNA (mRNA) vaccines and the vaccines utilizing a viral vector (non-replicating adenoviral strains) [4,5]. However, vaccines using inactivated SARS-CoV-2 strains have also been approved by the World Health Organization (WHO) and are available in many countries around the globe [6,7]. All types of the currently approved circulating vaccines have shown to be safe and effective in reducing the risk for severe COVID-19 infection [4,8]. Besides the common (and usually mild) side effects of the authorized vaccines, such as the low-grade fever and the pain at the injection site [8,9], some major, but thankfully, uncommon, adverse reactions are increasingly being reported during the post marketing surveillance phase [9]. Here, we briefly outline the most serious and/or rare complications of COVID-19 vaccines that have been described to date (see Table 1).

Anaphylaxis is a serious generalized allergic reaction that is characterized by rapid onset affecting the airway and/or the lower respiratory tract and/or the circulation, that may lead to death [10]. Anaphylaxis has been rarely reported after COVID-19 vaccination, with an estimated rate of 11.1 cases per million doses administered [11], with the mRNA based vaccines (BTN162b2 and mRNA-1273) being the two vaccines with the most frequently reported cases compared to the viral vector vaccines [11–13]. Although the potential causative allergens within the COVID-19 vaccines have not been identified yet, polyethylene glycol (PEG) and polysorbate might be implicated in severe allergic reactions associated with mRNA and vector-based vaccines, respectively [14]. The clinical features of severe immediate IgE-mediated hypersensitivity reactions to COVID-19 vaccines do not differ from other anaphylactic reactions; however, other mimicking conditions such as vasovagal episodes or anxiety-related symptoms should be discriminated from true anaphylaxis [15]. Laboratory tests like tryptase levels might be useful in difficult to differentiate cases [16]. The treatment of anaphylaxis does not differ from that of severe allergic

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reactions from other causes [17,18]. For the cases with confirmed moderate and severe allergic reactions after the first vaccine dose, the administration of the second dose is not recommended, or (in the case of an mRNA vaccine first) can be substituted by a non-mRNA vaccine [17,18].

In late February 2021, a syndrome called Thrombosis with Thrombocytopenia Syndrome (TTS) or Vaccine-induced Thrombotic Thrombocytopenia (VITT) was first reported in a small group of people in the United Kingdom (UK) who received the ChAdOx1 CoV-19 vaccine, an adenoviral vector-based vaccine developed by Astra Zeneca and the University of Oxford [19,20]. Later, similar cases of thrombosis with thrombocytopenia were also reported in individuals who were vaccinated with the adenoviral vector-based Ad26.COV2.S vaccine by Johnson & Johnson [21]. VITT usually occurs within 4–42 days following vaccination against COVID-19 and is characterized by the development of arterial and/or venous thrombosis (usually at atypical such as cerebral and abdominal thrombosis), along with low platelet count, high d-dimers (>4 times the upper limit of normal) and positive antibodies against the platelet factor 4 (PF4, positive PF4-heparin ELISA) [21]. Although a single case of VITT has also been reported post-vaccination with the mRNA-1273 vaccine that was developed by the Moderna company, the vast majority of these cases occur after administration of Ad26.COV2.S or ChAdOx1 CoV-19 vaccines; interestingly, other adenoviral vector-based vaccines (such as the Gam-COVID-Vac/Sputnik V by Gamaleya Institute) have not been implicated in the development of the syndrome [22]. The exact incidence of this novel entity remains unknown. However, it is estimated that it occurs in 0.73 per 100,000 individuals [95% confidence interval

Table 1
Characteristics of the serious complications caused by COVID-19 vaccines.

Vaccine Complications	Most Common Vaccine Type	Incidence	Possible pathogenetic mechanisms	Clinical presentation	Special Considerations for treatment or prevention
Anaphylaxis	mRNA vaccines (BNT162b2 and mRNA-1273)	11.1 cases per million doses	Immediate generalized IgE-mediated hypersensitivity reaction. Potential allergens: Polyethylene glycol (PEG) (mRNA vaccines) and polysorbate (vector-based vaccines)	Flashing, eruption, urticaria, angioedema, airway and/or breathing and/or cardiovascular compromise	For (confirmed) severe allergic reactions after the first vaccine dose, the Centers for Disease Control and Prevention (CDC) and the World Allergy Organization (WAO) recommend against the administration of second dose and maybe the substitution of an mRNA vaccine with a non-mRNA for the second dose
Vaccine-induced Thrombotic Thrombocytopenia	Adenoviral vector-based vaccines (ChAdOx1 CoV-19 and Ad26.COV2.S)	0.73 cases per 100,000 individuals	Activation of the platelets by the anti-PF4[a] antibodies, leading to arterial/venous thrombosis and platelet consumption	Arterial and/or venous thrombosis (usually cerebral and abdominal thrombosis) - Low platelet count, high d-dimers (>4 times upper limit of normal) and positive anti-PF4[a]antibodies	High dose IVIG[a] with or without corticosteroids and non-heparin anticoagulation-In refractory cases, plasma exchange and complement inhibition with eculizumab
Myocarditis/ Pericarditis	mRNA vaccines (BNT162b2 and mRNA-1273)	12.6 cases per million doses Highest among male adolescents and young adults	Molecular mimicry between the viral spike protein and a cardiac protein, as well as induction of immunologic pathways and a non-specific innate inflammatory response	Retrosternal chest pain, often worsened by inspiration and relieved by leaning forward and respiratory distress -High troponin and C-reactive protein levels - ST-segment elevation in the electrocardiogram - Mildly reduced to normal left ventricular ejection fraction and global hypokinesis in transthoracic echocardiogram - Abnormal findings in cardiac MRI	Non-steroidal anti-inflammatory drugs, colchicine and steroids - In patients ≤18 years old, intravenous immunoglobulin and steroids
Guillain-Barré syndrome	Adenoviral vector-based vaccines (ChAdOx1 CoV-19 and Ad26.COV2.S)	Ad26.COV2.S: 7.8 cases per million doses ChAdOx1 CoV-19: 227 cases per 51.4 million doses Highest among males aged 50–64 years	Acute or subacute immune-mediated neurologic disease of peripheral nerves that is usually triggered by vaccines - Molecular mimicry, anti-ganglioside antibody production and complement activation	Ascending weakness in limbs or cranial nerves, flaccid paralysis and areflexia - Distal paresthesia or quadriparesis with facial diplegia-Increased cerebrospinal fluid protein with normal numbers of cells	Steroids, IVIG[a] and/or plasma exchange
Acute Transverse Myelitis	Adenoviral vector-based vaccines (ChAdOx1 CoV-19)	Unknown (sporadic cases)	Immune-mediated neurologic disease that is usually triggered by vaccines - Molecular mimicry and bystander immune response activation	Quadriplegia or Paraplegia -Abnormal spinal cord MRI	Steroids, IVIG[a]
Acute Disseminated Encephalomyelitis	mRNA and Adenoviral vector-based vaccines	Unknown (sporadic cases)	Immune-mediated neurologic disease that is usually triggered by vaccines - Molecular mimicry and bystander immune response activation	Abnormal brain and spinal cord MRI - Clinical manifestations of Acute Disseminated Encephalomyelitis	Steroids, IVIG[a] and/or plasma exchange
Bell's Palsy	mRNA vaccines (BNT162b2 and mRNA-1273)	Unknown (sporadic cases)	Immune-mediated neurologic disease that is usually triggered by vaccines - Molecular mimicry and bystander activation of dormant autoreactive T-cells	Unilateral facial paresis or paralysis	Steroids
Rhabdomyolysis	mRNA and Adenoviral vector-based vaccines	Unknown (sporadic cases)	Exaggerated immune response to vaccine adjuvants	Myalgia, weakness and dark urine -High plasma creatine kinase levels and high urine myoglobin	Intravenous hydration -In severe disease, consider urinary alkalinization

[a] Anti-PF4: antibodies against platelet factor 4, IVIG: intravenous immunoglobulin.

(CI) 0.43–1.23] who receive the first dose of the ChAdOx1 CoV-19 vaccine [23]. The highest incidence has been reported in Norway, where it was estimated to be around 1 in 26,000 individuals [24]. The mortality of this condition is 1–2%, although in some series has been reported to be as high as 20% [21,25]. It was initially suggested that VITT affects predominantly young women (<60 years old); however, this has been questioned by subsequent reports showing no female sex predominance, while older individuals are also increasingly reported [26,27]. The exact pathogenetic mechanism of VITT remains unknown, albeit it is postulated that it resembles that of heparin-induced thrombocytopenia (HIT) by mimicking the effects of heparin on platelets through binding to a similar site on PF4 [28,29]. The anti-PF4 antibodies - that are formed through cross-reaction with vaccine's antigens - bound and activate the platelets leading to arterial and venous thrombosis and, consequently, to platelet consumption [28–30]. However, it should be noted that anti-PF4–polyanion antibodies are commonly found in other conditions (such as in up to 50% of post cardiac surgery patients) without leading to thrombosis; this phenomenon denotes that our understanding regarding VITT pathogenesis is still insufficient [25]. As it is an immune mediated condition, suggested treatment includes administration of high dose intravenous immunoglobulin (IVIG) with or without corticosteroids and non-heparin anticoagulation [21]. In refractory cases, plasma exchange and complement inhibition with eculizumab have also been used [21].

In June 2021, a possible causal association between SARS CoV-2 mRNA-based vaccines, both BNT162b2 vaccine and mRNA-1273 vaccine, and myocarditis and/or pericarditis, was reported [31]. Since then, there is increasing evidence thatmyocarditis and pericarditis constitute as rare complications of the mRNA vaccines [32]. As of August 18, 2021, Vaccine Adverse Event Reporting System (VAERS) has received 1339 reports of myocarditis or pericarditis among people <30 years old, who received COVID-19 vaccine, but through follow-up, Centers for Disease Control and Prevention (CDC) and FDA have confirmed 778 reports of myocarditis or pericarditis in male adolescents and young adults without any significant cardiovascular co-morbidities [33]. The estimated myocarditis/pericarditis rate was 12.6 cases per million doses of second-dose mRNA vaccine among individuals 12–39 years of age [34], while the adjusted risk ratio for myocarditis and pericarditis events in children and young adults between 16 and 24 years of age has been described to be 0.94 (95%CI 0.59–1.52) [34]. CDC recommendations clearly outline the benefits of COVID-19 vaccination, which outweigh the rare myocarditis and pericarditis risks and, therefore, it recommends the vaccination for anyone who is 12 years of age and older [34]. Although the pathophysiological mechanisms of myocarditis development are not clear, molecular mimicry between the viral spike protein and a cardiac protein, as well as induction of immunologic pathways and a non-specific innate inflammatory response have been proposed [31]. Most patients with post-vaccination myocarditis present retrosternal chest pain, that is often worsened by inspiration and relieved by leaning forward, while some patients develop respiratory distress in addition to the chest pain. Symptom onset is usually within 2–3 days (range 1–7 days) after the second dose of mRNA vaccination [31]. Laboratory investigations show elevation in troponin and C-reactive protein levels that are both indicative of myocardial inflammation. The electrocardiogram is abnormal, demonstrating ST-segment elevation, while transthoracic echocardiogram shows mildly reduced to normal left ventricular ejection fraction and global hypokinesia. Treatment includes non-steroidal anti-inflammatory drugs, colchicine and corticosteroids; in young patients (≤18 years old), IVIG (along with corticosteroids) has also been administered [35]. To date, all cases that have been reported in the literature, developed a non-severe disease with complete clinical recovery within 1–3 weeks post myocarditis/pericarditis onset [31,35].

Rare cases of Guillain-Barré syndrome (GBS) have been reported following vaccinations with adenovirus vector COVID-19 vaccines, such as Ad26.COV2.S and ChAdOx1 CoV-19 [36]. GBS is an acute or subacute immune-mediated neurologic disease of peripheral nerves that is usually triggered by infections and is characterized by ascending weakness in limbs or cranial nerves, flaccid paralysis and areflexia, as well as by increased cerebrospinal fluid protein with normal numbers of cells [37,38]. Within VAERS, 100 reports of GBS following Ad26.COV2.S vaccine were received from February 27th to June 30th, 2021 with approximately 12.2 million of doses administered [36]. The GBS reporting rate was 7.8 cases per million Ad26.COV2.S vaccine doses administered, while it was highest among males aged 50–64 years, with 15.6 cases per million Ad26.COV2.S vaccine doses administered. The median age of patients, who developed GBS after Ad26.COV2.S, was 57 years (range: 24–76), 61% were males, and the median interval between vaccination and symptom onset was 13 days (range: 0–75 days) [39]. Most patients presented clinical recovery and one patient died [39]. A total of 227 cases of GBS were reported after ChAdOx1 CoV-19 vaccine by June 27, 2021, with about 51.4 million doses administered [40]. A study that summarized the data of the patients with GBS after the ChAdOx1 CoV-19 vaccine, reported that all cases developed GBS following the first dose with a latency between 3 and 22 days [41]. The majority showed rare phenotypes such as distal paresthesia or quadriparesis with facial diplegia; the patients received steroids, IVIG and/or plasma exchange, with a partial recovery [41]. Sporadic cases of GBS have been also reported after the mRNA COVID-19 vaccines [42,43].

In total, 3 cases of acute transverse myelitis (ATM) were reported during the Phase III clinical trial of ChadOx1 CoV-19 vaccine, two in the vaccine arm and one in the control arm. The second patient with ATM among the two reported cases in the vaccine arm, was not vaccine-related as the patient was diagnosed with pre-existing multiple sclerosis [44]. Since then, random cases of ATM, as well as cases of acute disseminated encephalomyelitis have been described in the literature [45–47]. Besides ATM and acute disseminated encephalomyelitis, 7 cases of bell's palsy were reported among nearly 40,000 participants in the vaccine arm in the clinical trials investigating efficacy of BNT162b2 and mRNA-1273 vaccines, while only 1 case was reported in the placebo arm [48,49]. This incidence is 3.5–7 times higher than the incidence of general population [48,49]. During post market surveillance, only a few cases of facial palsy following COVID-19 vaccination have been described [50,51]. Finally, rare cases of vaccine-induced rhabdomyolysis have been reported [52]. However, it is worth noting that there is currently no evidence denoting a pathogenetic mechanism between COVID-19 vaccines and these entities.

In conclusion, COVID-19 vaccines are the mainstay for the prevention of this global pandemic. Despite rare cases of complications, the risk-benefit- assessment for COVID-19 vaccination shows a clearly favorable balance towards vaccines for all patients that vaccines have been approved irrespectively of age and sex. However, vaccine adverse events should be identified, monitored and followed up with high priority in order to manage them properly. The benefits of COVID-19 vaccines continue to outweigh any potential risk of adverse events. These complications should not be the reason of changing the vaccine policy and further studies are needed to alleviate public concerns and potential reluctance to COVID-19 vaccinations.

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Declaration of competing interest

None to declare.

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