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REVIEW

Incidence and management of the main serious adverse events reported after COVID-19 vaccination

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Abstract

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2n first appeared in Wuhan, China in 2019. Soon after, it was declared a pandemic by the World Health Organization. The health crisis imposed by a new virus and its rapid spread worldwide prompted the fast development of vaccines. For the first time in human history, two vaccines based on recombinant genetic material technology were approved for human use. These mRNA vaccines were applied in massive immunization programs around the world, followed by other vaccines based on more traditional approaches. Even though all vaccines were tested in clinical trials prior to their general administration, serious adverse events, usually of very low incidence, were mostly identified after application of millions of doses. Establishing a direct correlation (the cause-effect paradigm) between vaccination and the appearance of adverse effects has proven challenging. This review focuses on the main adverse effects observed after vaccination, including anaphylaxis, myocarditis, vaccine-induced thrombotic thrombocytopenia, Guillain–Barré syndrome, and transverse myelitis reported in the context of COVID-19 vaccination. We highlight the symptoms, laboratory tests required for an adequate diagnosis, and briefly outline the recommended treatments for these adverse effects. The aim of this work is to increase awareness among healthcare personnel about the serious adverse events that may arise post-vaccination. Regardless of the ongoing discussion about the safety of COVID-19 vaccination, these adverse effects must be identified promptly and treated effectively to reduce the risk of complications.

KEYWORDS
adverse effects, COVID-19, SARS-CoV-2, vaccines

Abbreviations: ACE2, Angiotensin-converting enzyme 2; ADEM, Acute disseminated encephalomyelitis; AIDP, Acute inflammatory demyelinating polyradiculoneuropathy; AMAN, Acute motor axonal neuropathy; AMSAN, Acute motor and sensory axonal neuropathy; Ad, Adenoviral; ACE2, Angiotensin-converting enzyme 2; APCs, Antigen-presenting cells; CMR, Cardiac magnetic resonance; CVST, Cerebral venous sinus thrombosis; CSF, Cerebrospinal fluid; CARPA, Complement activation-related pseudo allergy; COVID-19, Coronavirus disease 2019; dsRNA, Double-stranded RNA; DVT, Deep vein thrombosis; ECG, Electrocardiogram; EMG, Electromyography; ELISA, Enzyme-linked immunosorbent assay; EUL, Emergency Use Listing; FEU, Fibrinogen-equivalent units; GBS, Guillain-Barré Syndrome; HIT, Heparin-induced thrombocytopenia; IVIg, Intravenous immunoglobulin; LNPs, Lipid nanoparticles; LETM, Longitudinally extensive transverse myelitis; MRI, Magnetic resonance imaging; MHC, Major histocompatibility complex; MS, Multiple sclerosis; NMO, Neuromyelitis optica; NETs, Neutrophil extracellular traps; NCV, Nerve conduction velocity; PF4, Platelet factor 4; PEG, Polyethylene glycol; RAS, Renin-angiotensin system; RBD, Receptor binding domain; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TTS, Thrombosis with thrombocytopenia syndrome; TM, Transverse myelitis; VAERS, Vaccine Adverse Event Reporting System; VITT, Vaccine-induced thrombotic thrombocytopenia; WHO, World Health Organization.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in Wuhan, China late in December of 2019. Due to its rapid global spread, the outbreak was declared a pandemic by the World Health Organization (WHO) by March 2020.[1] Most infected individuals remained asymptomatic or had mild "flu-like" symptoms. However, some people, especially aged population and/or with comorbidities (obesity, diabetes, hypertension, lung disease), had severe manifestations of the disease, including pneumonia, acute respiratory distress syndrome and damage in extrapulmonary tissues (e.g., heart, kidney, gastrointestinal tract, and pancreas), therefore requiring hospitalization and intensive care.[2] As of 2 August 2023, there have been 6 953 743 deaths reported to the WHO.[3]

SARS-CoV-2 is a single-stranded positive-sense RNA virus, whose cell entry occurs via the receptor binding domain (RBD) of the Spike protein, one of the four structural proteins coded by its genome.[4] Spike displays on the virus surface as a trimer, comprises two subunits (S1 and S2), and has a furin cleavage site (S1/S2).[5] Virus entry requires the interaction of the receptor binding motif, present in RBD of S1, with the angiotensin-converting enzyme 2 (ACE2) of the host cells.[6] ACE2 is a plasma membrane glycoprotein with a broad tissue expression; lung has a moderate expression, while intestine, kidney, testis, heart, thyroid gland, and adipose tissue have the highest expression.[7,8] ACE2 is responsible for the conversion of angiotensin II (Ang II) to the heptapeptide Ang 1–7; thus its enzymatic function is critical for renin-angiotensin system (RAS) balance.[9]

In view of the global health emergency, vaccine development became a priority. In an extraordinary short time, two mRNA vaccines were first approved, BNT162b2 (Comirnaty) from Pfizer-BioNTech and mRNA-1273 (Spikevax) from Moderna. Then, two adenoviral vector vaccines came into scene, Ad26.COV2.S (Jcovden) from Johnson & Johnson (Janssen) and ChAdOx1 nCov-19 (Vaxzevria) from the University of Oxford and AstraZeneca. As of 30 March 2023, there were 183 vaccine candidates in clinical trials and 199 in preclinical studies.[10] Of those in clinical phase 3 or 4, only 11 vaccines were included in Emergency Use Listing (EUL) from the WHO.[11]

Common local side effects induced by most approved COVID-19 vaccines were pain and redness/swelling at the injection site, while the systemic side events more often reported were headache, fever, myalgia and fatigue.[12–23] The national and regional surveillance programs, as well as clinical and basic research projects around the world, have played an important role to gather, organize, and critically evaluate the incidence of side effects after vaccination.

Some adverse events, although very rare, are considered serious because of their potentially fatal outcome.[1] Among the more reported serious adverse events after COVID-19 vaccination are anaphylaxis, vaccine-induced thrombotic thrombocytopenia (VITT), myocarditis, Guillain–Barré Syndrome (GBS), and acute transverse myelitis (TM). Given its very low incidence, they were almost not observed during phase 3 clinical trials; their occurrence became evident after the massive worldwide vaccination programs. Hence, there are increasing numbers of case reports, retrospective cohort studies, systematic reviews, meta-analysis, and other studies, aimed to described them.

2 | MAIN PLATFORMS OF COVID-19 VACCINES

Most of the COVID-19 vaccines are based on Spike protein of SARS-CoV-2, since it is exposed on viral surface, mediates entry into host cells and thereby, is the main target of neutralizing antibodies upon infection.[5] Likewise, many of the vaccine candidates in clinical or preclinical studies are based on RBD of S1, intended for a more focused and safe immune response, as up to 90% of neutralizing antibodies target RBD.[24] An ideal vaccine should induce high levels of neutralizing antibodies, elicit robust Th1-biased immune responses, stimulate and maintain long-lasting immunological memory prior to the emergence of new variants, and provide cross-protection among various coronavirus strains and variants.[25]

Some COVID-19 vaccines (Table 1) include mutations that stabilize Spike protein in its pre-fusion conformation (prior to host cell attachment), in which it is more likely to generate protective antibodies, those targeting relevant epitopes present in S1 that can be hidden or lost on the Spike post-fusion conformation. There are two strategies to prevent this structural change: Spike protein with 2 residues (K986 and V987) mutated to proline (S-2P), and deletion/mutation of the S1/S2 furin cleavage site.[29] Different vaccine platforms and adjuvants differentially activate innate immune cells and inflammatory cytokines via specific signaling molecules and pathways, therefore influencing the quality and magnitude of adaptive immune responses.[30] We will briefly outline the main type of vaccines against SARS-CoV-2 in the next sections.

2.1 | Nucleic acid vaccines

Nucleic acid (DNA/RNA) vaccines carry a nucleotide sequence encoding the protein of interest. This approach uses the host cellular machinery to generate foreign antigens, which could be presented in the context of both major histocompatibility complex (MHC) class I and class II molecules from antigen-presenting cells (APCs), thereby eliciting both humoral and cellular immune.[31,32] DNA-based vaccines need to reach the cell nucleus; in contrast, mRNA-based vaccines induce a faster antigen expression since it occurs in the cytoplasm, which also avoids any risk of insertional mutagenesis. Issues of instability, high innate immunogenicity, and inefficient delivery have been solved through engineering RNA sequences and using highly efficient nanocarrier systems to mediate intracellular delivery.[31,32] To the latter purpose, the two approved mRNA vaccines employ lipid nanoparticles (LNPs), which have four components: an ionizable lipid, cholesterol, a helper phospholipid,

TABLE 1 Approved COVID-19 vaccines included in Emergency Use Listing by World Health Organization.

Vaccine platform	Vaccine name (efficacy)	Commercial name	Manufacturer (dosage regimen)	Immunogen	Notes
mRNA	BNT162b2 (95%)[12]	Comirnaty	Pfizer/BioNTech (2 doses)	S-2P	Ionizable cationic lipid: ALC-0315 Other lipids: DSPC, cholesterol, PEG-ALC-0159
	mRNA-1273 (94.1%)[13]	Spikevax	Moderna (2 doses)	S-2P	Ionizable cationic lipid: SM-102 Other lipids: DSPC, cholesterol, PEG-DMG
Viral vector	ChAdOx1 nCov-19 or AZD1222 (74%)[18]	Vaxzevria	University of Oxford/AstraZeneca (2 doses)	tPA.S	Vector: ChAdOx1 Produced in T-REx HEK293 cells
	Covishield (Oxford/Astra-Zeneca formulation)		Serum Institute of India (2 doses)		
	Ad26.COV2.S (52.9%–74.6%)[26]	Jcovden	Janssen (Johnson & Johnson) (1 dose)	S-2P, S1/S2 cleavage site mutations	Vector: Ad26 Produced in PER.C6 TetR cells
	Ad5-nCoV (57.5%)[15]	Convidecia	CanSino Biologics (1 dose)	tPA.S	Vector: Ad5 Produced in HEK293SF-3F6 cells
	Gam-COVID-Vac[a] (91.6%)[19]	Sputnik V	Gamaleya Research Institute (2 doses)	Spike	Vector: recombinant Ad5 and Ad26
Inactivated virus	CoronaVac (65.9%–67.7%)[27,28]		Sinovac Biotech (2 doses)	Whole virus	Vero cell cultivation β-propionolactone inactivation Aluminum hydroxide adjuvant
	BBIBP-CorV (72.8%–78.1%)[20]	Covilo	Sinopharm (2 doses)	Whole virus	Vero cell cultivation β-propionolactone inactivation Aluminum hydroxide adjuvant
	BBV152 (77.8%)[21]	Covaxin	Bharat Biotech (2 doses)	Whole virus	Vero cell cultivation β-propionolactone inactivation Algel-IMDG adjuvant
Protein subunit	NVX-CoV2373 (89.7%–90.4%)[16,17]	Nuvaxovid	Novavax (2 doses)	S-2P, S1/S2 cleavage site mutations	Baculovirus-insect cell expression system Saponin-based adjuvant (Matrix-M1)
	Covovax (Novavax formulation)		Serum Institute of India (2 doses)		

Abbreviations: DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; IMDG, imidazoquinoline; PEG, polyethylene glycol, usually bound to a lipid (PEGylated lipid, e.g., PEG-DMG and PEG-ALC-0159); PER.C6, human embryonic retinal cell line; S1/S2, between subunits 1 and 2 of Spike; S-2P, full-length Spike with two proline stabilizing mutations (K986P, V987P); tPA.S, fusion of tissue plasminogen activator signal peptide to Spike; T-Rex HEK293, variant from human embryonic kidney 293 cell line.

[a]Included just for comparative purposes, but not in Emergency Use Listing (restarted assessment).

and a PEGylated lipid, together encapsulating and protecting the fragile mRNA core.[33] Other advantages of mRNA vaccines are its fully synthetic nature, relatively rapid design, and production, as well as easy scalability. However, they also present some drawbacks such as high cost and requirement of an ultra-cold chain process for storage and distribution.[33,34]

Both mRNA-based vaccines, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), use the S-2P strategy to stabilize the prefusion Spike conformation (Table 1), and have demonstrated very high efficacy and good safety in phase 3 clinical trials.[12,13]

2.2 | Viral vector vaccines

Adenoviral (Ad) vectors used as a vaccine platform are inherently immunogenic and usually require no additional adjuvants.[35] So far, Ad vectors used by approved COVID-19 vaccines are non-replicating, because their viral replication genes had been deleted, and instead contain the coding sequence for the antigen of interest (i.e., Spike protein), whose expression occurs once inside the cells of the vaccinee.[36] Viral vector vaccines induce both humoral and cellular immunity.[35,37] Within this category, the WHO's EUL includes

ChAdOx1 nCov-19 (Vaxzevria, Oxford/AstraZeneca), Ad26.COV2.S (Jcovden, Johnson & Johnson/Janssen), and Ad5-nCoV (Convidecia, CanSino), while the status of assessment for Gam-COVID-Vac (Sputnik V, Gamaleya Research Institute) was restarted.[38]

In populations previously exposed to the most used Ad vectors like Ad5, a diminished immune response after vaccination could be a disadvantage. To avoid this potential issue, other human serotypes or non-human Ad vectors have been explored, such as Ad26 in Jcovden and the first dose of Gam-COVID-Vac, or chimpanzee Ad vector in Vaxzevria.[36,37] Other design aspects are a strategy to stabilize Spike in its trimeric form in two vaccines (Vaxzevria and Convidecia), which involves the fusion of Spike protein to the tissue plasminogen activator (tPA) signal peptide, and the use of S-2P approach in Jcovden[39] (Table 1).

2.3 | Inactivated virus vaccines

Inactivated virus vaccines are produced through the cell culturing of whole virus particles, which are made non-infectious by chemical (formaldehyde, β-propionolactone) or physical (heat, UV radiation) means,[40] while retain their capacity to stimulate the immune system. Compared with live-attenuated virus vaccines that also use whole viruses, inactivated virus vaccines are safer; however, they usually require an adjuvant, such aluminum hydroxide, to generate a robust cellular immune response.[41] The WHO has approved three vaccines in this category given their good efficacy and safety profile: CoronaVac (Sinovac), BBIBP-CorV (Covilo, Sinopharm), and BBV152 (Covaxin, Bharat Biotech) (Table 1).

2.4 | Protein subunit vaccines

Subunit protein vaccines contain one or few viral proteins, or even only a protein fragment (e.g., RBD) of the antigen, favoring their safer profile with respect to full pathogen-based vaccines (i.e., inactivated or attenuated virus), but also contributing to a reduced immunogenic capacity. Therefore, the use of adjuvants in their formulation and multiple doses are considered to enhance the immune response for this type of vaccines.[42] A protein subunit vaccine is produced in vitro, without the risks and special equipment associated to handling infectious live viruses. However, since many stages are required in its design and production, including purification steps, this type of vaccines may take longer than others to generate.[34,42] There are many recombinant expression systems available to produce the target protein, including bacterial, mammalian, yeast, insect and plant cells.[30] Protein-based vaccines usually are stable, safe, and well tolerated, even in elderly or immunodeficient individuals.[34]

NVX-CoV2373 (Nuvaxovid, Novavax) is the only protein subunit vaccine approved by the WHO to this date. It is a nanoparticle vaccine consisting of the prefusion-stabilized Spike protein (S-2P), produced with the baculovirus-insect cell expression system, and combined with the saponin-based Matrix-M adjuvant.[43,44] Serum Institute of India is producing Covovax using Novavax formulation. Overall, this vaccine has had very good efficacy and a favorable safety profile in various clinical trials.[16,17,44]

3 | COVID-19 VACCINES AND MAIN SERIOUS ADVERSE EVENTS

Serious adverse events following immunization include those that are life-threatening, require hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, give rise to congenital anomalies, or are medically important events or reactions.[45] These events are very rare and should be temporally associated with the vaccine administration, and before establishing a causal relationship, all other possibilities must be discarded, including simple coincidence or alternative origins in particular individuals. In the next sections, the serious adverse events most reported after COVID-19 vaccination are described, contemplating their incidence, risk factors, diagnosis, and treatment.

3.1 | Immunological adverse events

The clinical manifestations of allergic reactions to vaccines may range from mild cutaneous signs (urticaria, angioedema) and symptoms (itching) to life-threatening systemic anaphylaxis. There are different types of hypersensitive reactions, type I involves IgE-mediated immune responses and occurs rapidly after exposure to allergens, type II is mediated by IgG or IgM antibodies, type III involves the immune complexes, and type IV (or delayed reactions) is mediated by T lymphocytes.[46]

3.1.1 | Anaphylaxis

Anaphylaxis is an acute hypersensitivity reaction with multisystem involvement that can present as, or rapidly (minutes–hours) progress to, a severe life-threatening condition. It may occur following exposure to allergens from a variety of sources including food, insect venom, drugs, and immunizations.[47] The World Allergy Organization updated the clinical definition of anaphylaxis in 2020 to enhance recognition[48] (Table 2).

Soon after the start of COVID-19 vaccination programs with mRNA vaccines, cases of anaphylaxis appeared.[49,50] A meta-analysis including 26 337 421 recipients of Pfizer-BioNTech and Moderna vaccines estimated an overall prevalence of 5 anaphylactic cases per million doses, with more cases associated with BNT162b2 and greater prevalence in women, usually occurring within 30 min of inoculation.[72] Another meta-analysis considering also vector vaccines (Janssen and AstraZeneca/Oxford), reported that Ad26.COV2.S had the highest risk of anaphylaxis in the USA and European Union.[51] A study using data from the USA Vaccine Adverse Event Reporting System (VAERS)

TABLE 2 Main serious immunological, cardiac and hematological adverse events after COVID-19 vaccination.

Rare adverse event (identified risks)	Clinical presentation and diagnostic criteria	Proposed mechanisms	Vaccine platform(s) with more reported cases
Anaphylaxis (female, allergy history)	Acute presentation: minutes to hours ONE of these scenarios: 1. Acute skin and/or mucosa signs or symptoms (e.g., hives, pruritus, angioedema) AND (a) respiratory compromise, (b) hypotension/ end-organ dysfunction OR (c) severe gastrointestinal symptoms 2. Acute hypotension, bronchospasm, laryngeal closure/inflammation, even without typical skin involvement	Immune response to the PEGylated lipid of LNPs in mRNA vaccines or to polysorbate 80 in the formulation of viral vector vaccines	mRNA • Pfizer/BioNTech and Moderna[49–53] Adenoviral vector • Oxford/AstraZeneca and Janssen[51–53]
Myocarditis (young men and adolescents)	Probable diagnosis: Chest pain, maybe also fever and dyspnea, high levels of cardiac troponin and C-reactive protein, abnormal ECG with ST elevations Definitive diagnosis depends on findings suggestive of myocarditis on endomyocardial biopsy (Dallas criteria) or CMR imaging (Lake Louise criteria)	Immune response to LNPs, dsRNA impurities or mRNA in susceptible individuals (e.g., with pre-existing dysregulated immune pathways or inflammatory conditions) Molecular mimicry between Spike and α-myosin or other cardiac proteins Spike-like effect: ACE2 downregulation and alteration of RAS, overall leading to inflammation	mRNA • Pfizer/BioNTech and Moderna[54–63]
Vaccine-induced thrombotic thrombocytopenia (female particularly for CVST, more cases within 30–50 years old)	Clinical manifestations based on the location of thrombosis site(s), for example: neurologic symptoms (headache, visual disturbances, drowsiness), unexplained back or abdominal pain, swelling in a limb, petechiae, easy bruising or bleeding Diagnostic criteria: Symptoms onset 5–30 days post-vaccination (mostly first dose, up to 42 days in DVT) Thrombocytopenia (platelet count $<150\times10^9$/L) Thrombosis at atypical sites, primarily venous (CVST, splanchnic, portal, DVT, pulmonary embolism), but may also be arterial High levels of D-dimer (>4000 FEU) PF4 antibodies (ELISA and/or functional assay)	Production of autoantibodies anti-PF4 that activate platelets and lead to a prothrombotic signaling cascade, along with a vaccine-mediated pro-inflammatory medium and/or individual predisposition by genetic factors	Adenoviral vector • Oxford/ AstraZeneca[64–69] • Janssen[69–71]

Abbreviations: ACE2, angiotensin-converting enzyme 2; CVST, cerebral venous sinus thrombosis; dsRNA, double-stranded RNA; DVT, deep vein thrombosis; ECG, electrocardiogram; ELISA, enzyme-linked immunosorbent assay; FEU, fibrinogen-equivalent units; LNPs, lipid nanoparticles; CMR, cardiac magnetic resonance; PF4, platelet factor 4; RAS, renin-angiotensin system; ST, segment on ECG.

and European EudraVigilance, retrieved 8940 anaphylactic cases post COVID-19 vaccination (mRNA and vector vaccines) among more than 800 million doses administered, and estimated a mean reporting rate of 10.67 anaphylactic cases per million doses, below other vaccines analyzed, like rabies vaccine.[52] An assessment until January 2023 of the same pharmacovigilance systems estimated a lower incidence rate (8.96 anaphylaxis reactions/million doses) and found that vector vaccines had higher reporting rates than mRNA vaccines.[53]

Hypersensitive reactions, including anaphylaxis, can be IgE-mediated or non-IgE-mediated.[73] IgE-mediated is the most studied, its occurrence on first exposure is not typical,[74] and there is usually sensitization by a prior antigen exposure. IgE-antigen complex interacts with receptor FcεRI on mast cells or basophils, which triggers their degranulation and release of inflammatory cytokines and other mediators, like histamine and prostaglandins, thereby inducing distinct systemic immune responses.[46] Non-IgE mediated anaphylactic responses, previously known as anaphylactoid reactions, have a similar clinical presentation as IgE-mediated reactions,[47,74] hence being as life-threatening if not promptly recognized and treated. In contrast, non-IgE mediated reactions may occur on first exposure to the antigen by direct activation of mast cells and basophils, stimulation of the complement system, or other pathways.[74]

The mechanisms involved in vaccine-induced anaphylaxis have not been elucidated but are of special interest, as vaccine platforms that have been associated with anaphylactic cases are those more recently approved for use in humans (mRNA and viral vectors). Therefore, safety issues must be considered facing their potential broad applications in medicine.

Immediate hypersensitive reactions to vaccines have been mainly attributed to non-active ingredients or excipients.[75] In the case of

mRNA-based COVID-19 vaccines, both Comirnaty and Spikevax use LNPs as delivery systems. The PEGylated lipid, which is a lipid with a polyethylene glycol (PEG) covalently bound, apports stability to these LNPs. PEG is a flexible hydrophilic polymer used in drug formulation to reduce clearance and prolong circulation time.[76] However, PEGylation has been related to hypersensitive reactions and induction of anti-PEG antibodies.[77] Whether they are induced by PEG per se or as a conjugated molecule, is not clear.[76] A recent study that measured anti-PEG IgE in serum samples from individuals who presented anaphylaxis after COVID-19 mRNA vaccines, did not find a difference respect to the control group, suggesting that anti-PEG IgE may not be directly related to anaphylactic cases,[78] which agrees with previous observations.[79] Nonetheless, PEG could provoke allergic reactions through other pathways, such as complement activation-related pseudo allergy (CARPA).[79,80] For viral vector vaccines (Vaxzevria and Jcovden), polysorbate 80, a non-ionic detergent that shares structure similarities with PEG, has been highlighted as a potential trigger of hypersensitive reactions.[75,80] Although, studies are needed to support this hypothesis.

To explain that anaphylaxis and other hypersensitive reactions were more observed in women, the impact of hormonal differences over allergic immunological responses has been proposed to play a role. Likewise, sensitization to PEG is most likely to occur in women due to their frequent exposure to PEG-containing products, such as cosmetics and contraceptives.[81]

A history of previous allergic reaction to vaccines or its components should be established before immunization.[73] Anaphylaxis following vaccination is rare in all age groups and must be distinguished from a vasovagal reaction, which is a common non-immune immediate reaction. Vasovagal reaction typically manifests with diaphoresis, nausea, vomiting, pallor, and bradycardia, in contrast to the flush, pruritus, urticaria, angioedema, tachycardia, and laryngeal edema presented in anaphylactic reactions.[74] To investigate about the underlaying mechanisms of anaphylaxis, it is useful to measure serum tryptase levels within 2 h after the event. A significant increase from baseline (at least 48 h later) is a strong indicator of mast cell as the source of inflammatory mediators.[73,74]

The first line of treatment is adrenaline. Expert medical staff and equipment to attend anaphylaxis (adrenaline, antihistamines, oral/parenteral steroids, and beta-2-inhalers) should be always available in vaccination units.[73] Identification of the culprit antigen in the vaccine formulation would be ideal to avoid future expositions in other products or future immunizations, as well as contribute to understanding the vaccine-induced anaphylactic mechanisms. Further genome analysis could aid in the identification of genomic markers in individuals with predisposition to anaphylactic reactions, who may not be candidates for vaccination.

3.2 | Cardiac adverse events

3.2.1 | Myocarditis and/or pericarditis

Among cardiac complications, myocarditis/pericarditis was the most common adverse event reported following COVID-19 vaccination, particularly after mRNA vaccines.[54] Myocarditis is an inflammatory disease of the myocardium (without ischemic involvement) that can be caused by infectious agents (virus, bacteria, protozoa, and fungi) or non-infectious stimuli (e.g., toxic substances, medications, and systemic autoimmune disorders).[82,83] Pericarditis, the inflammation of the pericardium or tissue overlying the heart muscle, sometimes coexists with myocarditis. Myocarditis and/or pericarditis, often referred as myopericarditis, has been reported after smallpox vaccination.[84]

Based on a large vaccination program in a health care organization of Israel (more than 2.5 million persons 16 years of age or older), myocarditis incidence within 42 days after receiving BNT162b2 was of 2.13 cases per 100 000 immunizations. The highest incidence (10.69 cases per 100 000) was estimated for males between 16 and 29 years old.[85] Although the specific numerical estimate of myocarditis incidence varies across different countries and populations, the greatest risk for young males, mostly after the second dose of both mRNA vaccines (Comirnaty and Spikevax), has been confirmed by many reviews of case reports and series,[54–57,86–88] by large-data analysis of passive surveillance programs such as VAERS, UK Yellow Card scheme, EudraVigilance or others,[58,89–91] and by systematic reviews and meta-analysis.[59,60,92] The risk has been extended to male adolescents.[93,94] More events were reported with mRNA-1273 immunization compared to BNT162b,[58,60,61,91,95] and shorter interdose intervals.[91]

A priming of immunological response or an increased susceptibility to vaccination is compatible with myocarditis mainly occurring after the second dose, or in some cases following the first dose but with a prior event of myocarditis or SARS-CoV-2 infection.[56,57,62,63] Myocarditis predominance in males is probably related to the effect that sex hormone differences have in cardiac physiology and immune responses,[96] and a possible underdiagnosis of cardiac disease in women.[54]

The mechanism by which myocarditis is induced by mRNA vaccines is not clear, but various hypotheses have been raised, for example, molecular mimicry between Spike and human cardiac self-proteins such as actin and α-myosin,[97] immune-inflammatory responses to residual quantities of double stranded RNA,[98] or to mRNA (despite nucleoside modifications) in susceptible individuals, genetic predisposition to autoimmune reactions, or preexisting dysregulated immune pathways.[54,99,100]

Other hypothesis suggests that some of the Spike protein or related peptide fragments coded by mRNA vaccines could escape into the systemic circulation[101] and reach the heart, where ACE2 is abundant. Free-floating Spike may also come from vaccine-targeted cells destroyed by the immune system.[102] The interaction of Spike with ACE2 would drive the receptor internalization and degradation, and the diminished ACE2 enzymatic activity could result in Ang II overactivity and Ang 1–7 deficiency, ultimately leading to platelet aggregation, thrombosis, inflammation, or other pathological symptoms that resemble those of SARS-CoV-2 infection.[102,103] This model is supported by a recent study that analyzed gene expression in cardiac biopsies from patients with myocarditis post COVID-19 and

post mRNA vaccination, as well as in control tissue.[104] Interestingly, nearly identical alteration of the mRNA expression was found in myocarditis samples associated to viral infection or vaccine administration, including a significant downregulation of ACE2 and upregulation of ACE and F3 (coagulation factor III or tissue factor); these mRNA changes could predispose to inflammation, coagulopathy, and myocardial dysfunction.[104]

Due to the diversity of clinical symptoms, aetiologies, and outcomes (e.g., heart failure, sudden death, and dilated cardiomyopathy), myocarditis diagnosis represents a challenge[105,106]; subclinical acute presentations and bias towards myocardial ischemia or infarction could partly explain underdiagnosis.[61] In the context of myocarditis post COVID-19 vaccination, most studies have based their conclusions on a level of suspected or probable certainty, given that confirmed or definitive myocarditis requires cardiac magnetic resonance (CMR) imaging and/or endomyocardial biopsy.[83,105] The latter is considered the diagnostic gold standard, but its indication is very limited in mild presentations due to its invasiveness, the probability of false negative results for localized myocardial injury and variability in histopathological interpretation.[105] CMR represents a non-invasive option, however, it also requires a high level of experience to be performed and analyzed.[105,106]

Myocarditis symptoms related to COVID-19 vaccination start very quickly, within 7 days after second vaccine dose in most cases, are of mild and benign clinical course, and have a rapid remission.[58,63,94] The most frequent symptom related to myocarditis following mRNA vaccines has been chest pain, and in a lower percentage, fever, dyspnoea and others.[55,57,85] Blood tests usually revealed high levels of troponin (consistent with myocardial injury) and inflammatory markers like C-reactive protein, as well as abnormal findings on the electrocardiogram suggestive of myocarditis, such as ST segment elevations.[55,57,85,86,94,107] In patients who underwent an echocardiogram, a preserved ventricular systolic function was mainly seen, only some of them presented evidence of subtle dilated wall or minor pericardial effusion.[107]

Myocarditis management depends on the severity, clinical presentation, and etiology[83]; it is focused on restoring hemodynamic stability and the control of heart failure and arrhythmia if needed.[86] Since vaccine-related myocarditis tends to be mild and with preserved ventricular function, reported treatment was mainly based on nonsteroidal anti-inflammatory drugs, and in a few cases colchicine, steroids or IVIg in addition.[55,57,87] When left ventricular systolic dysfunction is involved, β-blockers, ACE inhibitors, angiotensin-receptor blockers, or diuretics may also be considered.[83]

3.3 | Hematologic adverse events

3.3.1 | Vaccine-induced thrombotic thrombocytopenia

Vaccine-induced thrombotic thrombocytopenia (VITT), also named thrombosis with thrombocytopenia syndrome (TTS), is a rare but severe new condition that resembles heparin-induced thrombocytopenia (HIT), particularly in the generation of antibodies that bound platelet factor 4 (PF4).[64–66] HIT is caused by the transient production of platelet-activating antibodies of the IgG class that recognize multimolecular complexes of PF4 (cationic) bound to heparin (polyanionic).[108] Autoimmune HIT, a variant that does not involve heparin or other pharmacologic trigger, is associated with a prothrombotic disturbance, and shares more clinical features with VITT.[64]

Early in 2021, VITT cases started to appear after administration of Oxford/AstraZeneca vaccine in the UK and many European countries, the majority of them involving clots in the brain (cerebral venous sinus thrombosis, CVST) with thrombocytopenia.[64–66] In the USA, VITT cases were described in recipients of Ad26.COV2.S vaccine.[70] The first 220 cases of VITT in the UK after millions of doses of ChAdOx1 nCoV-19 were documented by Pavord et al.,[67] estimating an approximate incidence of 1:50 000 among patients of less than 50 years of age, and of 1:100 000 among older patients, with no sex predominance; 49 were fatal cases (22%). Following massive application of Ad26.COV2.S in the USA, the TTS reported rate (VAERS) was estimated in 3.83 cases per million doses, being the highest among women aged 30–49.[71]

True incidence of VITT is difficult to establish as the literature is constantly evolving.[109] Besides, there is a possible underreporting in countries where Ad vector vaccines were widely administered, but with limited resources to diagnose VITT (e.g., Mexico, India), although a role of ethnicity could be explored.[110]

As VITT after COVID-19 vaccination has been associated with Oxford/AstraZeneca and Janssen vaccines, the main hypothesis for the pathophysiology mechanisms points to a role of Ad vectors. A greater incidence of VITT with ChAdOx1 nCoV-19 compared to Ad26.COV2.S has been attributed to differences between vaccine composition (e.g. excipients such EDTA, Ad genetic material, residual proteins of adenovirus, and production cells). A study found that ChadOx1 nCoV-19 promotes a stronger pro-inflammatory milieu, given its higher proportion of proteins from the production cells (T-REx HEK293) and the use of a non-human Ad vector compared to Ad26.COV2.S.[111]

PF4, a tetrameric chemokine stored in α-granules of platelets, is released in the plasma upon platelet activation and can bind to polyanionic molecules, including negatively charged surfaces of microbial pathogens. This interaction induces conformational changes in PF4, exposing different epitopes, and anti-PF4 antibody-producing B cells are likely part of an innate immune protection mechanism.[112] In VITT, it has been hypothesized that bloodstream PF4 binds the highly anionic Ad vector capsid (hexon) and other vaccine constituents, generating neoantigens that along with the pro-inflammatory environment promotes the formation of pathogenic autoantibodies anti-PF4.[112,113] Double stranded DNA leaked from the Ad vector vaccine at the injection site may provide another highly negative element for PF4 interaction.[114] Once produced, high affinity "VITT anti-PF4 antibodies" promote PF4 clustering on the platelet surface, and the crosslinking of FcγRIIA receptors leads to

platelet activation with the resultant release of PF4 and procoagulant platelet microparticles.[113,115]

Antibodies observed in VITT also seem to stimulate neutrophils to release neutrophil extracellular traps (NETs), which have a procoagulant activity.[113] Given that VITT is not observed in all vaccination cases with Ad vector vaccines, there might be an individual predisposition for the development of VITT. It has been suggested a genetic component[116,117] and/or a previous priming of a subset of B cells to produce pathogenic anti-PF4 antibodies. The time window of clinical presentation after vaccination fits more with a secondary immune response, and main thrombosis sites, such cerebral venous sinuses and splanchnic veins, receive nasal sinus or intestinal drainage, which may allow access of microbiota and viral products.[114,118]

Clinical manifestations of VITT depend on the thrombosis sites. Thromboses usually involved multiple vascular beds, from both venous and arterial circulation; their primary location has been the cerebral venous sinus, but thrombosis was also observed in portal-, splanchnic- and deep-vein, pulmonary embolism, and arterial events in peripheral vasculature, heart, and brain.[67] There could be neurologic symptoms (headache, visual disturbances, and drowsiness), unexplained back or abdominal pain, swelling or redness in a limb, petechiae, easy bruising, or bleeding, among others.[68] Diagnostic criteria include the onset of symptoms 5–30 days after COVID-19 vaccination (Vaxzevria and Jcovden), thrombosis in atypical sites, thrombocytopenia, high D-dimer levels, and positive ELISA (Enzyme-linked immunosorbent assay) for PF4 antibodies (Table 2). The VITT case is considered definitive if all five criteria are met and probable if one is missing.[67,115] High D-dimer and low fibrinogen levels suggest systemic activation of coagulation.[119]

VITT treatment is based on anticoagulation agents and reducing the autoimmune response. Anticoagulant options include parenteral direct thrombin inhibitors (bivalirudin, argatroban), oral factor Xa inhibitors (apixaban, rivaroxaban), and fondaparinux.[64] Parental agents are preferred in the acute/critical phase but can be switched to oral ones in subacute and chronic phases.[115] Heparin is not recommended due to VITT similarities with HIT, however it was safe in cases where it was used.[67] It would be riskier to delay the treatment than to give heparin if no other anticoagulant is available. Thrombocytopenia is not a contraindication to therapeutic anticoagulation; in fact, patients with the lowest platelet counts could be at higher risk of thrombosis. The duration of anticoagulant treatment is still unclear, but usually is prescribed while platelet count is low and D-dimer is high.[120] To inhibit Fcγ receptor-mediated platelet activation, intravenous immunoglobulin (IVIg) at a high dose (1 g/kg, 1–2 days) is indicated. Steroids (prednisone, dexamethasone) are a choice if IVIg is not accessible; vitamin K antagonists, aspirin, and routine transfusions should be avoided in acute VITT.[120] In severe cases, plasma exchange may help clearing autoantibodies. Monoclonal antibodies rituximab and eculizumab may be used when other therapies fail.[121]

3.4 | Neurological adverse events

Neurological mild adverse events are commonly observed after COVID-19 vaccination, including headache, anosmia, dizziness, myalgia, paraesthesia, and weakness[122]; regularly are of short duration, self-limiting and ambulatory manageable.[123] While neurological serious adverse events are rare and may involve the central and/or peripheral nervous system (e.g., brain, cranial nerves, spinal cord, and peripheral nerves); they usually require hospitalization or supportive care. Among these are Bell's palsy, Guillain–Barré Syndrome (GBS), transverse myelitis (TM), and cerebral venous sinus thrombosis.[123–125] The recovery time from these events is variable as many factors have an influence, for example, patient's characteristics (sex, age, comorbidities), opportune and appropriate diagnosis and treatment, disease severity, and potential complications.

3.4.1 | Cerebral venous sinus thrombosis

Although CVST is a rare cerebrovascular condition, in young adults it is an important cause of stroke, with higher incidence in women. Among risk factors are pregnancy, medications (e.g., oral contraceptives), infections (e.g., otitis, meningitis), head trauma, inherited thrombophilia, autoimmune systemic diseases, and cancer.[126] Since CVST is the most common type of VITT, possible pathophysiological mechanisms and general aspects were described in the previous section. CVST association with thrombocytopenia, as in VITT, is very unusual before COVID-19 pandemic.[127] Almost all cases of CVST have occurred following first doses of Ad vector vaccines ChAdOx1 nCoV-19 and Ad26.COV2.S.[67,69,70] Interestingly, CVST has also been reporter after SARS-CoV-2 infection,[128] however studies comparing CVST presentation after infection and vaccination are lacking.

Clinical presentation of CVST is diverse and depends on the affected sinus location, patient age, time between onset and hospital admission, and the presence of parenchymal lesions.[129] The most common symptom is headache, which may be diffused or localized, usually refractory to analgesics; other clinical scenarios include isolated intracranial hypertension (that can lead to headache, papilledema and/or visual impairment), seizures, focal neurological deficits (hemiparesis, aphasia, visual loss), subacute encephalopathy (mental and alertness disturbances, particularly if deep veins are involved), and multiple cranial neuropathies (cavernous sinus syndrome).[127,130] CVST may cause brain tissue edema due to impaired venous drainage, that in turn could affect the delivery of oxygenated blood or provoke weakening of capillary walls, potentially conducting to ischemia or venous hemorrhage, respectively.[121]

When CVST is suspected, urgent imaging of the brain and its venous system is required for diagnosis, for example, computed tomography (CT), or magnetic resonance imaging (MRI), with venography in either case.[130] The goal is to assess and prevent complications like intracerebral hemorrhage and stroke. A systematic review of VITT with CVST case reports and series showed a high

rate of intracerebral hemorrhage.[69] Management recommendations are the same as for VITT, but complementary symptomatic treatment (e.g., antiepileptics, osmotic therapy, lumbar puncture, and acetazolamide) should be consider if needed.[129] Importantly, attention must be paid to the so-called pre-VITT syndrome (i.e., VITT without thrombosis), in which some patients present a persistent headache and fulfill all the diagnostic criteria of VITT (previous section) except for the presence of thrombosis on imaging studies.[131] In these cases, VITT treatment (i.e., anticoagulation and IVIg) is strongly suggested to prevent the disease progression, in contrast, CVST development has occurred when treatment was delayed or stopped prematurely.[131,132]

3.4.2 | Guillain–Barré syndrome

GBS is an inflammatory heterogeneous disease of the peripheral nervous system, characterized by rapidly progressive weakness of legs and/or arms with hypo- or areflexia. GBS is the most common cause of acute flaccid paralysis.[133,134] GBS is a rare disease, the estimated incidence ranges from 0.81 to 1.89 cases per 100000 persons/year in North America and Europe; it increases with age and males have a higher risk than females.[135] The main known trigger is a previous bacterial or viral infection by *Campylobacter jejuni*, cytomegalovirus, *Mycoplasma pneumoniae*, among other pathogens.[136–138] GBS is particularly remembered by its controversial association with influenza A (H1N1) vaccine during the "swine flu" immunization program of 1976 in New Jersey/US.[139] Subsequently, there have been GBS reports following application of vaccines against rabies, polio, tetanus, hepatitis B, and others; however evidence to establish a causal association is little.[140]

In the context of COVID-19 pandemic, there have been reports of GBS, both after SARS-CoV-2 infection and following vaccination,[124,141,142] although for an association to be established or discarded, more studies are required. GBS was mainly reported after Ad vector vaccines from Oxford/AstraZeneca and Janssen, and in a lesser extent following mRNA vaccines. During clinical trials, only Janssen registered a GBS case in the vaccine group, although another one occurred in the placebo group also.[26] The analysis of surveillance data from US Vaccine Safety Datalink, including 15.1 million doses of COVID-19 vaccines from December 2020 to November 2021, found an elevated risk of GBS after Ad26.COV2.S (significantly higher than pre-pandemic background rate) but not following mRNA vaccines.[143] A more recent study, using VAERS data and considering a longer period (to January 2022), arrived at the same conclusion about a possible association between Jcovden and GBS, with a reporting rate of 4.07 cases per 100000 in a post-vaccine window of 6 weeks compared to less than 0.5 for BNT162b2 and mRNA-1273.[144] In Australia, GBS cases reported between February and November 2021 were analyzed, confirming 41 cases within 42 days post-vaccination (Vaxzevria $n=38$, Comirnaty $n=3$, Spikevax $n=0$); most cases (35) occurred after the first dose. The estimated incidence was 1.85 cases per 100000 doses, which exceeded the expected background rate of 0.39.[145]

Moreover, the analysis of immunoglobulin-treated GBS cases registered after COVID-19 vaccination by the UK National Immunoglobulin Database between January and October 2021 found a GBS excess risk of 0.58 cases per 100000 first doses of ChAdOx1 nCoV-19 within 6 weeks after vaccination, but not an incidence excess with first doses of mRNA vaccines.[146] While a large prospective surveillance study, carried out in a province of South Korea considering 38 million doses of SARS-CoV-2 vaccines from February 2021 to March 2022, estimated an overall incidence of 1.42 per million doses and a higher risk associated with vector-based vaccines (Vaxzevria and Jcovden) than with mRNA vaccines (Pfizer and Moderna).[147]

Interestingly, Ad5-vectored vaccines are not related with an increased risk of GBS, such as Convidecia (CanSino) and Sputnik V, perhaps due to a protective role of preexisting immunity.[148] In general, more GBS cases were registered in men than in women,[144,146,147] like GBS background epidemiology[135] and following SARS-CoV-2 infection.[141,142] Vaccine-related GBS cases occurred in a wide range of ages, but more events were observed between 50 and 69 years old individuals.[144,146]

Demyelination and/or axonal degeneration by GBS is considered autoimmune-mediated, resulting in nerve damage or functional blockade of nerve conduction.[134] Molecular mimicry between gangliosides (sialic acid-containing glycosphingolipids enriched in peripheral nerves) and a microorganism component (e.g., lipopolysaccharides of the outer membrane of *C. jejuni*) has been the most studied underlying mechanism, sustained by the detection of differential anti-ganglioside autoantibodies (e.g., anti-GM1, GD1a, GT1a, GQ1b) in certain GBS subtypes and variants.[136,138] In the context of post COVID-19 vaccination, the pathophysiological mechanism is not clear, but it has been proposed that antibody cross-reactivity between SARS-CoV-2 Spike protein and peripheral nerve glycolipids[149] or proteins related to myelin/axon homeostasis,[150] may be involved in causing demyelination or axonal damage. Additionally, a genetic background of the host (e.g., polymorphisms in human leucocyte antigen genes) could confer an increased susceptibility for a neurological autoimmune disorder,[151] as observed for SARS-CoV-2 infection and GBS development.[152] Other hypotheses considered are the contribution of certain adenovirus (ChAdOx1 and Ad26) to the invasion of the peripheral nervous system, or the generation of anti-vector antibodies with cross-reacting potential with host molecules related to myelin or axons.[148] A dual contribution in the case of vector vaccines is not discarded, such as the combination of the Spike protein and Ad vector (e.g., proinflammatory nature), which could lead to a stronger immune response in susceptible individuals and hence GBS development, compared to just the Spike with mRNA vaccines.

The classical clinical presentation of GBS includes sensory symptoms, such as paraesthesia, numbness, or pain. The main GBS subtypes are acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). When both motor and sensory fibers are affected, the subtype is named acute motor and sensory axonal neuropathy (AMSAN).[134] Apart from the classical sensorimotor GBS, there are clinical variants and atypical

presentations; for example, in the paraparetic variant, weakness is restricted to the legs, and Miller Fisher syndrome comprises ophthalmoplegia, areflexia and ataxia. GBS variant limited to the cranial nerves may manifest as bilateral facial palsy with paraesthesia, while pure sensory or pure motor GBS variants also exist. Classical sensorimotor GBS is the most frequent presentation (30%–85%), followed by the pure motor variant (5%–70%), Miller Fisher syndrome (5%–25%) and the paraparetic variant (5%–10%).[133]

Disease progression is very rapid, and nadir (higher disability or severity) occurs within 2 weeks (maximum 4 weeks), reaching a plateau phase of variable duration (weeks to months) before recovery starts.[133,134] Mortality (3%–7%) usually occurs due to the involvement of autonomic nervous system, which can lead to respiratory failure and/or cardiovascular complications (e.g., cardiac arrhythmias and blood pressure instability). Therefore, GBS progression should be closely monitored to prevent and manage complications.[134,137]

GBS cases following COVID-19 vaccination were diverse, but classical sensorimotor presentation and AIDP subtype predominated.[141,147,153] Bilateral facial weakness or paralysis was also a frequent encounter after Oxford/AstraZeneca and Janssen vaccination according to some GBS case series and reports.[149,154–156] The severity of GBS was variable, depending on damage extent to the motor, sensory and autonomic nerve fibers of the spinal roots, and peripheral and/or cranial nerves. Most cases reported a good outcome after treatment, nonetheless some individuals had a partial improvement or poor outcome.[144]

GBS diagnosis is based on clinical (including neurological), electrophysiological (electromyography, nerve conduction velocity), and cerebrospinal fluid (CSF) examinations. It is recommended to start treatment, even before test results arrive, if one of these conditions is present: inability to walk 10 m independently, rapid progression of weakness, severe autonomic or swallowing dysfunction, or respiratory insufficiency.[133] Commonly, there is albuminocytologic dissociation (i.e., normal cell counts and high protein levels) in the CSF.[138] Nerve conduction studies help to confirm the presence, pattern and severity of the neuropathy and distinguish between demyelinating and axonal GBS subtypes.[136,137]

Effective treatments include IVIg (0.4 g/kg body weight for 5 days, preferably within 2 weeks from onset) or plasma exchange (200–250 mL plasma/kg in 5 sessions).[133] Supportive care is important and involves monitoring of respiratory function, as well as cardiac and hemodynamic parameters, prophylaxis for deep vein thrombosis, management of possible bladder and bowel dysfunction, and early initiation of physiotherapy and rehabilitation. Despite treatment, many patients develop severe weakness and have a long disease course, often with incomplete recovery, pain, and fatigue.[137]

3.4.3 | Transverse myelitis

Transverse myelitis (TM) is a neurological disorder characterized by inflammation of the spinal cord that results in sensory, motor and autonomic dysfunction; its presentation can be acute or subacute and is associated with a diversity of aetiologies, such as infections (herpes virus type 2, varicella-zoster virus, cytomegalovirus, etc.), demyelinating diseases, systemic inflammatory autoimmune syndromes, paraneoplastic or vascular conditions, and vaccination.[157,158] TM cases have been reported after hepatitis B, rubella, diphtheria-tetanus, and rabies vaccines, among others, but a causal relationship has only been supported for oral polio vaccine.[159]

TM incidence is between 1.34 and 4.6 per million yearly, with peaks between ages 10–19 and 30–39 years, and no gender predisposition.[160] During an interim analysis of clinical trials of ChAdOx1 nCoV-19 vaccine, three cases of TM were reported, one in the control group, one attributed to previously unrecognized multiple sclerosis (MS), and only one likely vaccine-related.[161] Most TM cases reported in the literature have occurred following mRNA or vector viral vaccines.[162] In a systematic review of the literature, Ostovan et al.[163] identified 31 TM cases post COVID-19 vaccination (17 females and 14 males); most of them (24) came after the first dose. For Oxford-AstraZeneca vaccine, there were more cases (12), followed by Pfizer (8), Moderna (7), Sinopharm (3), and Janssen (1). About 70% of patients had a good recovery; prognosis worsened with age and second dose, and although it was apparently more common in women, sex was not an outcome predictor.[163] Supporting a possible link of TM and COVID-19 vaccines, an observational and retrospective study based on VigiBase, the WHO's pharmacovigilance database, analyzed 500 individual case reports of TM between December 2020 and March 2022, considering 28 days as post-vaccination limit to the onset of TM symptoms.[164] The largest number of cases were reported after BNT162b2 (280), followed by ChAdOx1 nCoV-19 (95), mRNA-1273 (84), and Ad26.CoV2.S (42). Nguyen et al.[164] suggested that despite the limitations of the study, including that incidence estimation could not be obtain because the lack of the exact number of individuals exposed to each vaccine, the statistical analysis favored an association between TM and both, mRNA-based (Pfizer and Moderna), and viral-vector based (AstraZeneca and Janssen) vaccines.

TM was not only registered after COVID-19 vaccination but also following SARS-CoV-2 infection; in the latter context, neurological symptoms/signs seem to be more severe, reach the nadir in a shorter time, and be of higher occurrence in males.[163] Differences may be due, at least in part, to the magnitude of the stimulus, which is expected to be higher for infection than for vaccines. The potential vaccine-induced mechanism has not been elucidated but molecular mimicry of Spike or Ad vector proteins with self-antigens (e.g., myelin) has been suggested.[162,163] Another mechanism to explain the development of autoimmunity is bystander activation, which could be induced by a vaccine component like the adjuvant (e.g., mRNA per se, Ad vector). Bystander activation involves the unspecific (antigen-independent) activation of autoreactive lymphocytes ($CD8^+$ T, $CD4^+$ T, B cells) without T or B cells receptors (TCR/BCR) stimulation, instead mediated by signals that promote an inflammatory milieu, for example, ligands of co-stimulatory receptors, cytokines, and pathogen-associated molecular patterns.[165] In the case of RNA-based vaccines, mRNA

may bind pattern recognition receptors before translation, such as Toll-like receptors TLR7 and TLR8, which could activate many pro-inflammatory cascades,[166] enhancing cytokine production and further expansion of autoreactive T cells.[167] Moreover, a pathogenic role of interleukin-6 (IL-6) has been found in myelitis,[168] and administration of both mRNA and viral vector vaccines induces an increase of several inflammatory markers, including this cytokine.[169]

The most common sign of TM is fever; early symptoms include a combination of sensory dysfunction (e.g., loss of thermal sensation), paraesthesia and/or pain in the back or extremities, motor weakness (usually ascending) of the lower limbs. Autonomic dysfunction is manifested mainly as urinary retention/incontinence or bowel disturbances. The progressive worsening of symptoms could take hours to days; nadir usually is reached at 7 days (up to 21), when at least two thirds of patients are unable to walk because of severe paraparesis or paraplegia.[158]

The importance of TM early identification lies in its debilitating/incapacitating effects, which could lead to a permanent disability.[167] For TM diagnosis is central to demonstrate that the characteristic clinical dysfunctions (usually bilateral) are originating from the spinal cord (Table 3); other diagnostic criteria are a defined sensory level and motor impairment progression to nadir between 4 h and 21 days.[157] Since TM has been associated with SARS-CoV-2 infection, it is essential to test for it. Differential diagnosis also would discard other probable infections (through specific serologic studies, CSF culture, PCR, chest radiography, etc.), neoplastic conditions, demyelinating diseases of the central nervous system like MS and neuromyelitis optica (NMO), among other causes of TM.[157] A few cases of longitudinally extensive transverse myelitis (LETM), comprising three or more vertebral segments, have been reported too after AstraZeneca vaccine.[171–173]

Acute treatment of TM is based on administration of intravenous glucocorticoids to oppose the gene expression of inflammatory mediators, thus preventing a further damage to the spinal cord.[158,170] In post COVID vaccination TM, a high dose of intravenous methylprednisolone (1 g daily for 3–7 days) is recommended.[174] When a refractory response occurs to a high dose of corticosteroids, plasma exchange can be helpful to remove autoreactive antibodies especially within 20 days of symptoms onset.[158] For example, a patient with LETM positive to MOG antibodies did not respond to corticosteroids but to plasma exchange.[173] In non-responsive cases, immunosuppressive therapy of T and B cells with cyclophosphamide maybe beneficial.[158]

TABLE 3 Main serious neurological adverse events after COVID-19 vaccination.

Rare adverse event (identified risks)	Clinical presentation and diagnostic criteria	Proposed mechanisms	Vaccine platform(s) with more reported cases
Guillain–Barré Syndrome (Male > female, more cases within 50–69 years old, genetic predisposition)	Bilateral rapidly progressing weakness of limbs with hypo- or areflexia, possibly along with sensory symptoms (paresthesia, numbness, pain). Other manifestations in GBS variants depending on the affected limbs (paraparesis) or cranial nerves (e.g., facial palsy, ophthalmoplegia) Symptoms onset within 42 days after vaccine (mostly first dose) CSF analysis: albuminocytologic dissociation (before treatment start) EMG and NCV studies indicative of a GBS subtype: demyelinating (AIDP) or axonal (AMAN, AMSAN)	Autoimmune process that leads to demyelination and/or axonal degeneration: Molecular mimicry of Spike or adenoviral vector component with myelin or axon-related proteins	Adenoviral vector • Oxford/AstraZeneca[124,141,145–147,149,154,156] • Janssen[143,144,147,153,155]
Transverse myelitis (prognosis worsens with age)	Fever, extremities or back pain, sensory deficits, bilateral motor (limb weakness, mostly progressive ascending) and autonomic dysfunction (bladder, bowel) Spinal cord involvement (without compressive lesion) observed in MRI (T2 hyperintense signal) Spinal cord inflammation: gadolinium enhancement in MRI, CSF pleocytosis or high abnormal protein Rapid progression to nadir: 4–21 days Exclusion of other causes: infectious, neoplastic, systemic and autoimmune, nutritional, vascular	Autoimmune-mediated: Molecular mimicry and/or bystander activation	mRNA and Adenoviral vector[162–164,170] • Pfizer/BioNTech and Moderna • Oxford/AstraZeneca and Jansen LETM • Oxford/AstraZeneca[171–173]

Abbreviations: AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy; CSF, cerebrospinal fluid; EMG, electromyography; GBS, Guillain–Barré syndrome; LETM, longitudinally extensive transverse myelitis; NCV, nerve conduction velocity; MRI, magnetic resonance imaging.

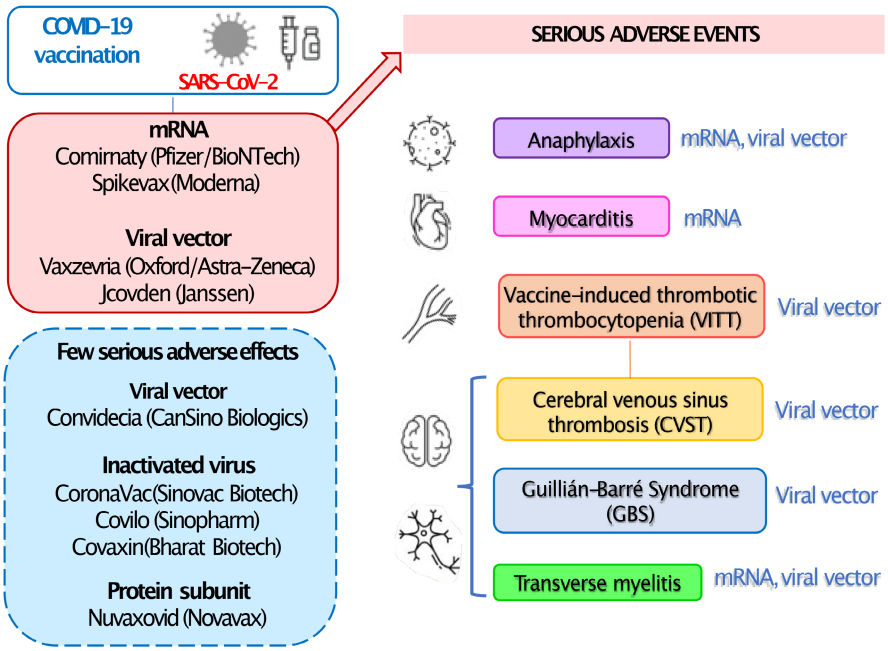

FIGURE 1 Main serious adverse events after COVID-19 vaccination. Scheme summarizing the more reported serious adverse events in immune, cardiovascular, and nervous systems after massive administration of approved vaccines against SARS-CoV-2. There have been anaphylaxis and myocarditis cases after mRNA vaccines Comirnaty and Spikevax, while VITT (including CVST) and GBS cases after viral vector vaccines Vaxzevria and Jcovden. To a lesser extent, transverse myelitis has been registered for both viral vector and mRNA platforms. In contrast, serious adverse events documented after administration of inactivated virus and protein subunit vaccines have been few overall.

3.4.4 | Other neurological serious adverse events

Other neurological adverse events have been registered with a lower incidence. In the continuum of TM, further demyelinating pathologies such as NMO and MS have been documented after COVID-19 vaccines.[162] Likewise, new-onset seizures, encephalopathy, acute disseminated encephalomyelitis (ADEM), myasthenia gravis exacerbation, herpes zoster (onset/relapse), among others.[125,174] Many of these disorders have been related with vaccines against other pathogens too[174]; however, most of the available studies are based on a small sample size, and temporal association is not sufficient to establish a causal association. The underlying mechanism potentially triggered by COVID-19 vaccines is unknown, but a combination of vaccine-related factors and susceptibility of the patients could be involved.[162]

4 | DISCUSSION

The aim of this review is to highlight the main serious adverse events that may be associated with the COVID-19 vaccines already massively applied (Figure 1). It is premature to establish a causal relationship given that other criteria, such as consistency of evidence, strong statistical association, and specificity, should also be considered before establishing a causal relationship.[175] However, there has been significant advancement in many of these parameters, particularly through the valuable epidemiological and medical data collection by international and national surveillance systems, presented in case reports and series, and analyzed by diverse studies (e.g., retrospective, or prospective cohorts, systematic reviews, and meta-analysis). Likewise, basic and clinical research studies of the pathophysiological mechanisms have made good progress. Hopefully, that will lead to a better understanding of these adverse events, their interactions and predisposition factors, which in turn will be useful to improve COVID-19 vaccine design and safety profiles. The goal would be to limit as much as possible the negative scenarios potentially related with each vaccine platform. Up to now, as many others have mentioned, the benefit of COVID-19 vaccination far exceeded the risks, since most of the population has not manifested these serious conditions and instead, millions of lives have been saved. Nonetheless, efforts to monitor and register the negative cases following vaccination, through surveillance and health systems, must continue.

When these serious adverse events are of mild to moderate severity, full or partial recovery can be expected if treatment is opportune. As shown in this review, some adverse events are more frequent with specific COVID-19 vaccines platforms (Tables 2 and 3; Figure 1); this information can be helpful for vaccine selection or recommendation to specific population groups, especially if booster doses are required in the future. Some of these adverse events were observed after SARS-CoV-2 infection too, usually with higher incidence or severity (e.g., myocarditis, GBS, TM). Many factors are involved when severe adverse events are presented after vaccination, in which the vaccine (e.g., platform, antigen, formulation) and host characteristics (e.g., genetic background, sex, age, comorbidities, and environment), interact to promote the manifestation of a particular event, especially those of autoimmune origin.

Given that all COVID-19 vaccines with a wide application around the world are based on Spike protein, one could think that differences in number of cases relate to the rest of the components in their formulation. However, it is difficult to establish strict and true comparations between data from different populations and vaccine platforms, and obviously it is important to consider that a higher number of doses have been administered for some of them. So far, the potential association between Ad vector vaccines and VITT seems to be the most sustained by large epidemiological data. Interestingly, Ad5-based vaccine CanSino has poorly been related to

this serious adverse event, suggesting that Ad vector type has also an influence to take into consideration.

A stronger immune response is important for the vaccine efficacy, but in people with a weakened/exacerbated immune system or with chronic health problems and comorbidities, adverse effects may occur more likely with some vaccine platform than with others. Therefore, physicians should be aware of the possible serious adverse events related to COVID-19 vaccines, to recognize them and make an early diagnosis.

Compared with COVID-19 vaccines based on Ad vector (Oxford/AstraZeneca and Janssen) and mRNA (Pfizer/BioNTech and Moderna) vaccines, serious adverse events incidence following inactivated (Sinovac, Sinopharm and Bharat) and protein subunit (Novavax) vaccines have been much lower so far (Figure 1). Therefore, although mRNA and vector vaccines offer advantages and higher efficacy, they might still need further improvements.

5 | CONCLUSION

The close onset of adverse events following COVID-19 vaccination suggests an association, however, a causal relationship cannot only be sustained on temporality. Meanwhile, it is prudent to keep vigilant about its incidence and mechanisms, as the literature is quickly evolving. The identified risk factors for the development of each serious adverse event addressed here in the context of COVID-19 vaccination, as well as their predominant occurrence with certain vaccine platforms, could be useful for the decision making on which vaccine is more suitable on an individual and health status basis.

AUTHOR CONTRIBUTIONS

TP-F did the literature search, designed, wrote, and edited the manuscript. LV conceived the idea, supervised, reviewed, and edited the manuscript. AS supervised and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Authors declare that this work is original and has not been published elsewhere. For this review no animal or human experiments were conducted.

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