At the Cutting Edge

The Impact of COVID-19 and Vaccine on the Human Nervous System

Fei Chen   Pingdong Cao   Huimin Liu   Dechen Cai

Department of Physiology, Jining Medical University, Jining, China

Abstract

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has precipitated a global health crisis of unprecedented proportions. Due to its severe impact, multiple COVID-19 vaccines are being developed, approved, and manufactured rapidly. However, some serious adverse events (AEs) were reported after the application of them, significantly increasing concerns about the safety and efficacy of the vaccines and doubts about the necessity of vaccination. Particularly, previous vaccination campaigns have shown us that partial vaccination can induce neurologic AEs. Herein, we discuss in depth the involvement of the nervous system during SARS-CoV-2 infection or after vaccination. On the one hand, CO-VID-19 could pose an enormous threat to human neurological health through direct infection and indirect neurotoxicity effects. On the other hand, our review indicated that only a few serious neurological AEs following vaccination occurred and among which headache was the most common. Moreover, some neurological AEs do not seem to be related to vaccination. Of course, the causal relationships between several vaccines and AEs are considered plausible, and it is not doubtful that these AEs should be taken seriously by clinicians in assessing the potential risks and benefits of vaccinations in special populations. Nevertheless, in the case of the rapid spread of COVID-19, the potential side effects of vaccination on the nervous system should be compared with adverse COVID-19 outcomes rather than being considered alone. Thus, it is obviously a wise option to be vaccinated instead of suffering from serious adverse symptoms of virus infection.

© 2022 S. Karger AG, Basel

Introduction

The novel coronavirus pandemic, which began in 2019, has exerted a devastating effect on society, economics, and public health around the world. In addition, mutations in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome make the control of the epidemic more complicated. Currently, the coronavirus disease 2019 (COVID-19) has caused more than 400 million confirmed cases, including more than 5 million deaths [1]. As a countermeasure, the speed of COVID-19 vaccine development is unprecedented. According to World Health Organization (WHO), more than 143 vaccine candidates are currently in clinical trials, and 9 of them (AstraZeneca/Oxford Vaccine, Johnson and Johnson, Moderna, Pfizer/BioNTech, Sinopharm, Sinovac,

Correspondence to:
Fei Chen, chenfei0336@163.com

Table 1. List of neurological AEs associated with vaccination

Neurological AE	Vaccine against	Reference
TM	Influenza, polio, rabies, rubella	[8–11]
GBS	Influenza	[12]
PTS	HBV	[13]
Narcolepsy	Influenza	[14]
ADEM	Rabies, DTP, smallpox, measles, mumps, rubella, JBE, pertussis, influenza, HBV, hog	[15]
MS	Influenza, HBV	[16, 17]
Neuromyelitis optica	HPV	[18]

TM, transverse myelitis; HBV, hepatitis B virus; HPV, human papillomavirus; DTP, diphtheria-tetanus-polio; JBE, Japanese B encephalitis; GBS, Guillain-Barré syndrome; PTS, Parsonage-Turner syndrome; ADEM, acute disseminated encephalomyelitis; MS, multiple sclerosis.

Bharat Biotech BBV152 COVAXIN, Covovax, and Nuvaxovid) have been granted emergency use authorization. However, during the past few months, serious adverse effects such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis, and thrombocytopenia were reported after vaccinations, and some cases have even proved fatal [2]. Immediately, some countries suspended the inoculation of several vaccines. These events sparked an intense societal and scientific debate on whether the benefits of existing vaccines outweigh the potential risk of unknown adverse events (AEs). It should be noted that the situation is bound to cause hesitation about vaccination, or more extreme anti-vaccine sentiment, which will become an obstacle to achieving adequate vaccination coverage.

As is well known, nervous system complications are a significant determinant of COVID-19 severity. The earliest reports from Wuhan found that 36.4% of patients showed a certain extent of neurological involvement, and which included central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, and epilepsy), peripheral nervous system (PNS) manifestations (anosmia, hypogeusia, visual impairment, and neuralgia), and skeletal muscular damage [3]. In a cohort study of 3,744 patients with clinically diagnosed or laboratory-confirmed COVID-19 at 28 centers, neurological manifestations were found in approximately 80% of patients; the most common self-reported symptoms included headache (37%) and anosmia or ageusia (26%), whereas the most common neurological signs and/or syndromes were acute encephalopathy (49%), coma (17%), and stroke (6%) [4]. More seriously, some of the above symptoms still bothered many survivors at 1 year after discharge from hospitals, 10.4% of them suffered from anxiety, 2.3% from headache, 1.4% from taste change, and 1.3% from impaired sense of smell [5]. Recently, by searching literature relative to thyroid dysfunction in patients with COVID-19, Scappaticcio et al. [6] have suggested that the entire hypothalamic-pituitary-thyroid axis could be the target of damage by COVID-19. Specifically, it could manifest as thyrotoxicosis, hypothyroidism, as well as nonthyroidal illness syndrome [6]. Moreover, the level of serum adrenocorticotropic hormone was significantly increased in COVID-19 patients compared to normal controls, but was dramatically decreased in critical cases compared to noncritical patients [7]. Therefore, it is essential to pay attention to the health of the nervous system and neuroendocrine function during the COVID-19 pandemic. Based on the results of previous mass vaccination campaigns [8–18], we made a comprehensive summary table (Table 1) that contains the neurological AEs following vaccinations. A part of these events is considered to be associated with vaccine-specific immune responses, which may derive from the stimulation of vaccine itself or adjuvant. Generally, in comparison with nonadjuvanted vaccines, adjuvanted vaccines can cause more local reactions (e.g., swelling, redness, and injection site pain) and more systemic reactions (e.g., chills, fever, and body aches). Of note, in order to accelerate the development of COVID-19 vaccines, many new platforms previously not widely used such as protein subunit, mRNA, DNA, and virus-like particle are applied, which may further increase the possibility of unknown neurological AEs after vaccination. Due to the unprecedented mass vaccination, an insignificant increase in the incidence of the side effects will also have a major impact on public health. Therefore, there is an urgent need to review the limited data and theoretical consider-

ations for informing clinical guidelines and our understanding regarding the various effects of COVID-19 and vaccines on nervous system.

Neurological Involvement of COVID-19: From Neuroinvasion to Neuroimmune Crosstalk

An ultrastructural autopsy performed within 3 h of death from COVID-19 demonstrated severe and widespread damage in the olfactory nerve, gyrus rectus, and medulla oblongata [19]. Moreover, Remmelink et al. [20] found 8 cases with cerebral hemorrhage or hemorrhagic suffusion, three with focal ischemic necrosis, five with edema and/or vascular congestion, and 10 with diffuse or focal spongiosis in 17 adult patients with COVID-19. It is worth noting that they also detected SARS-CoV-2 RNA in 9 of the 11 cerebral samples [20]. Similarly, according to a statistical analysis of 25 papers [21], the positive result was also obtained in cerebrospinal fluid from 6.4% (30/468) patients, among which 21 presented symptoms that localized in the CNS and 3 had PNS symptoms such as Guillain-Barré syndrome (GBS). Based on the detection of SARS-CoV-2 in the olfactory mucosa/nerve/bulb and clinical-neurological signs related to alterations in smell and taste perception, it was assumed that SARS-CoV-2 enters the CNS through the olfactory pathway. However, most studies reporting an infection of olfactory neurons only displayed a few images showing isolated olfactory neurons possibly co-located with the virus, and semiquantitative analyses showed that the SARS-CoV-2 was mainly located in Bowman's gland cells and sustentacular cells [22, 23], while olfactory neurons did not contain virus or contain very few [22, 24–26]. The only quantification was made in human angiotensin-converting enzyme 2 mice, and the authors found only a small population of immature olfactory sensory neurons (1.28%) and mature olfactory sensory neurons (0.03%) were infected by SARS-CoV-2 [27]. Moreover, virus-infected olfactory epithelium has been shown to contain dying neurons [28], which can be phagocytosed by sustentacular cells [26, 29]. Thus, the viral protein of the infected sustentacular cell may generate false positives. Taken together, the brain infection in COVID-19 is unlikely to be through the olfactory nerve, but through other routes such as the hematopoietic pathway via the blood-brain barrier, retrograde axonal transport through the other cranial nerves, and so on.

Notably, among the 13 cases of classic GBS that associated with SARS-CoV-2 infection, pulmonary involvements were very mild and the results of SARS-CoV-2 test in cerebrospinal fluid were negative [30]. Thus, not all neurological symptoms require direct infection of the nervous system. Indirect neurotoxicity can be secondary to immune-mediated pathogenesis [3, 31]. In SARS patients, it has been reported that autoantibodies binding to endothelial cells and epithelial cells could induce some of these cell lyses [32]. Similarly, in COVID-19 patients, antibodies against the virus may also attack antigens of endothelial cells in cerebral vessels. In addition, gastrointestinal infection poses another threat to the nervous system, as it may increase the transport of aberrant proteins like α-synuclein which are associated with neurodegenerative diseases [33]. More importantly, nerve injury leads to abnormal intestinal blood flow and intestinal dysmotility, which could further promote bacterial components and metabolites' entry into the blood and brain parenchyma, aggravating brain damage [34]. By the way, the therapeutic potential of multiple drugs used for other diseases leads to the off-label use for COVID-19, such as corticosteroids, antiretroviral drugs (remdesivir, lopinavir-ritonavir, and darunavir), biological treatments (tocilizumab), and antibiotics (azithromycin), but some of which have been shown to induce neurologic and psychiatric symptoms. As mentioned in our previous paper, peripheral administration of dexamethasone could induce biphasic effects on anxiety-related behaviors and cerebral edema [35]. Recently, gastrointestinal hemorrhage and psychosis are deemed to be related with dexamethasone treatment in the RECOVERY trial [36]. Apart from this, lopinavir could cause disruption of astrocytic glutamate homeostasis and was associated with neurobehavioral deficits and gliosis in mice exposed to oral doses [37]. Likewise, suramin treatment (which is at least 20-fold more potent than remdesivir in inhibiting SARS-CoV-2 RNA-dependent RNA polymerase activity) could lead to Ca2+ dyshomeostasis in dorsal root ganglia neurons and subsequently a predominantly sensory axonal-demyelinating neuropathy [38].

Systemic and Neurological AEs following Vaccinations

To obtain the literature of COVID-19 vaccine trials, we used the WHO COVID-19 vaccine tracker and landscape. Meanwhile, the PubMed database and Google Scholar were searched from database inception to February 2022 for all articles in any language using "COVID-19 vaccine," "safety," "efficacy," "randomized," "clinical tri-

al," and clinical trial number (including NCT, ChiCTR, PACTR, ISRCTN, CTRI, EUCTR, NL, jRCT, RPCEC, IRCT, ACTRN, and PER) as keywords. We excluded reviews, letters, editorials, study protocols, animal studies, case reports, and meeting abstracts. Then, the literature was screened by the following criteria: (1) healthy participants older than 16 years; (2) a sample size of at least 100 participants; (3) randomized controlled design; and (4) the most recent study phase. A total of 33 studies met the inclusion criteria [39–71], and we extracted the vaccine platform, name, location, age, study phase, sample size, and safety data (especially the neurological AEs) from the included clinical trials (Table 2). Moreover, it must be noted that vaccine-unrelated AEs as specified in the articles have been excluded.

From Table 2, we can see that serious AEs occurred at a higher frequency in RNA groups, especially mRNA-1273. Pain, fever, and headache are the most commonly reported grade III and IV AEs after vaccine administration. Among them, the headache following COVID-19 vaccination is not similar to the headache after other previous vaccinations. The constellation of accompanying symptoms along with the temporal and spatial headache characteristics delimits its unique phenotype [72]. In terms of other neurological AEs, they presented more often among nonreplicating viral vector vaccine and RNA vaccine recipients in the clinical trial phase, and of note, more types were identified in mass vaccination campaigns (Table 3) [73–84]. It is considered reasonable because some diseases are too rare for such events to be observed in hundreds to tens of thousands of subjects. Moreover, clinical development programs are designed to explore the benefits of vaccines, with demonstration of efficacy being the primary goal of standard vaccine trials. Vaccine safety assessment is generally considered as a secondary objective, and pivotal randomized clinical trials are not powered to enable statistical analyses of endpoints of specific AEs. Only after vaccination is administered in large populations after licensure is it possible to observe several uncommon AEs. Further, some AEs could be more complex and difficult to identify, especially those of COVID-19 vaccines produced utilizing new technologies.

Nonreplicating Viral Vector Vaccine

According to Table 1, GBS could be triggered by influenza vaccination. Similarly, although seeing only 1 case among numerous Ad26.COV2.S recipients (Table 2), Sa-

doff et al. [43] considered it was associated with vaccination. During the mass vaccination campaigns, the Food and Drug Administration has issued a statement that Ad26.COV2.S might trigger a rare neurological condition in a small number of people, and the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommended adding a warning about GBS to the label of the vaccine to inform health care providers. It is easy to understand because the secreted IgG might cross-react with surface epitope in the PNS similar to SARS-CoV-2 spike glycoprotein or aberrant splice variants [85], thereby activating the complement system and leading to nerve cell membrane damage and destruction. In addition, vaccination results in T cell activation and differentiation into a T helper cell type 1 or Th2 phenotype. Once inside the PNS, the T helper cell type 1 would recruit and activate macrophages, which could initiate damage to PNS by producing and secreting nitric oxide and matrix metalloproteinases. Most importantly, most adults have been infected by multiple adenovirus types. When injected with the adenovirus vector vaccine, the anti-adenoviral effector memory T cells will be reactivated. By the way, in cases of GBS after AZD1222 vaccination, there were marked differences in clinical patterns and sex ratio across countries. Most patients were male in the UK, with most developing distal dysesthesia and a few of them having quadriplegia. In contrast, all patients developed quadriplegia and the majority of them were female in India [73]. Thus, it is necessary to further investigate the effect of nonreplicating viral vector vaccination on the development of GBS in people with various genetic backgrounds and whether specific subpopulations have a higher risk.

A new type of AEs called thrombosis with thrombocytopenia syndrome (TTS) has been detected in a small number of individuals who received the Ad26.COV2.S or AZD1222 vaccine. According to WHO, the causal relationship between these vaccines and TTS is considered plausible. In 72% of initial TTS reports, CVST was noted and may be associated with special blood flow condition in this area. This result is not difficult to understand, since the study by Kowarz et al. [86] has shown that the splice reactions in adenovirus-based vaccines could result in spike protein variants that lack the transmembrane anchor and thus may become secreted due to the nature of the secretory pathway. Moreover, the nonunidirectional blood flow in the venous vessels of CNS sinuses could prolong the residence time of variants, thereby increasing the probability of binding to endothelial cells expressing ACE2. Notably, Ad26.COV2.S appears to carry fewer

Table 2. Grade III and IV AEs of COVID-19 vaccines in the latest clinical trials

Vaccine platform	Vaccine	Location	Age	Study phase	Sample size (vaccine group vs. placebo group)	Grade III and IV AEs except neurological AEs (cases, n)	Grade III and IV neurological AEs (cases, n)	Reference
Nonreplicating viral vector	AZD1222	US, Chile, and Peru	≥18	3	32,451 (21,635 vs. 10,816)	Fever (DNP), chills (DNP), muscle pain (DNP), malaise (DNP), tenderness (DNP), and fatigue (DNP)	Chronic inflammatory demyelinating polyradiculoneuropathy (1), hypoesthesia (1), and headache (DNP)	[39]
	Ad5-vectored COVID-19 vaccine	Argentina, Chile, Mexico, Pakistan, and Russia	≥18	3	36,717 (18,363 vs. 18,354)	Fever (27), drowsiness (66), nausea (15), diarrhea (7), vomiting (1), generalized muscle aches (65), redness (4), swelling (3), and pain (49)	Headache (85)	[40]
	Sputnik V	Russia	≥18	3	21,977 (16,501 vs. 5,476)	None	None	[41]
	Ad26.COV2.S	Belgium, Brazil, Colombia, France, Germany, The Philippines, South Africa, Spain, UK, and US	≥18	3	31,300 (15,708 vs. 15,592)	Injection site swelling (1), pyrexia (1), hemoptysis (1), pulmonary embolism (1), pericarditis (1), vertigo (1), allergy to vaccine (1), increased myocardial necrosis marker (1), nausea (2), fatigue (1), vaccination site erythema (1), acute sinusitis (1), localized infection (1), and myalgia (1)	Cerebrovascular accident (1), headache (1), and facial paresis (1)	[42]
		Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and US	≥18	3	43,783 (21,895 vs. 21,888)	Fatigue (2), chills (1), malaise (1), pyrexia (1), nausea (2), diarrhea (1), dyspepsia (1), vomiting (1), myalgia (1), vaccination site hypersensitivity (1), pain in extremity (1), tendon disorder (1), pericarditis (1), post-vaccination syndrome (1), tachycardia (1), and nasal congestion (1)	Guillain-Barré syndrome (1), syncope (1), Bell's palsy (2), brachial radiculitis (1), and headache (4)	[43]
RNA	mRNA-1273	US	≥18	3	30,415 (15,209 vs. 15,206)	Pain (606), erythema (287), swelling (255), axillary swelling (68), fever (216), fatigue (1,433), myalgia (1,321), arthralgia (775), nausea (22), and chills (191)	Headache (666), cerebrovascular accident (1), and syncope (1)	[44]
	BNT162b2	Argentina, Brazil, South Africa, Germany, Turkey, and US	≥16	2/3	44,165 (22,085 vs. 22,080)	Fever (DNP), fatigue (DNP), chills (DNP), vomiting (DNP), diarrhea (DNP), pain (DNP), redness (DNP), swelling (DNP), shoulder injury (1), right axillary lymphadenopathy (1), paroxysmal ventricular arrhythmia (1), and right leg paresthesia (1)	Headache (DNP)	[45]

Table 2 (continued)

Vaccine platform	Vaccine	Location	Age	Study phase	Sample size (vaccine group vs. placebo group)	Grade III and IV AEs except neurological AEs (cases, n)	Grade III and IV neurological AEs (cases, n)	Reference
RNA	CVnCoV	Belgium, Germany, The Netherlands, Spain, Argentina, Colombia, Dominican, Republic, Mexico, Panama, and Peru	≥18	2/3	39,680 (19,846 vs. 19,834)	Pain (10), swelling (1), fatigue (176), myalgia (99), chills (135), arthralgia (40), fever (67), nausea (6), diarrhea (5), acute myocardial infarction (1), atrial fibrillation (1), cardiac arrest (1), supraventricular extrasystoles (1), ventricular tachycardia (1), appendicitis (1), and cellulitis (1)	Headache (143) and seizure (1)	[46]
	ARCoV	China	18–59	1	120 (100 vs. 20)	Injection site pain (1) and fever (22)	None	[47]
Inactivated	CoronaVac	Brazil	≥18	3	12,408 (6,201 vs. 6,207)	None	None	[48]
		Turkey	18–59	3	10,218 (6,650 vs. 3,568)	Systemic allergic reaction (1)	None	[49]
		Chile	≥18	3	434 (270 vs. 164)	None	None	[50]
	WIV04	UAE and Bahrain	≥18	3	26,941 (13,470 vs. 13,471)	Pain (6), induration (1), swelling (1), fever (28), diarrhea (12), constipation (1), vomiting (3), myalgia (9), arthralgia (2), dyspnea (7), pruritus (4), skin and mucosal abnormalities (1), and fatigue (11)	Headache (14)	[51]
	HB02	UAE and Bahrain	≥18	3	26,941 (13,470 vs. 13,471)	Emesis (1), pain (1), rash (1), itching (1), fever (23), diarrhea (8), constipation (1), dysphagia (1), vomiting (3), nausea (1), myalgia (8), arthralgia (2), dyspnea (6), pruritus, (1) and fatigue (19)	Headache (13)	[51]
	SARS-CoV-2 vaccine (vero cells)	China	18–59	2	750 (600 vs. 150)	None	None	[52]
	QazCovid-in®	RK	≥18	3	3,000 (2,400 vs. 600)	None	None	[53]
	BBV152	India	18–98	3	25,798 (12,899 vs. 12,899)	DNP	DNP	[54]
	KCONVAC	China	18–59	2	500 (400 vs. 100)	None	None	[55]
	NDV-HXP-S	Thailand	18–59	1/2	210 (175 vs. 35)	None	None	[56]
	CoviVac	Russia	18–60	1/2	398 (298 vs. 100)	None	None	[57]

Table 2 (continued)

Vaccine platform	Vaccine	Location	Age	Study phase	Sample size (vaccine group vs. placebo group)	Grade III and IV AEs except neurological AEs (cases, n)	Grade III and IV neurological AEs (cases, n)	Reference
Protein subunit	NVX-CoV2373	UK	18–84	3	15,187 (7,593 vs. 7,594)	Myocarditis (1), fatigue (DNP), malaise (DNP), muscle pain (DNP), joint pain (DNP), elevated temperature (DNP), pain (DNP), tenderness (DNP), erythema (DNP), and swelling (DNP)	Headache (DNP)	[58]
		US and Mexico	≥18	3	29,949 (19,965 vs. 9,984)	Pain (302), tenderness (837), erythema (143), swelling (91), fatigue (1,423), malaise (1,082), muscle pain (846), joint pain (417), fever (64), and nausea (36)	Headache (518)	[59]
	ZF2001	China	18–59	2	900 (600 vs. 300)	Redness (6), swelling (3), injection site pain (1), induration (1), rash (1), and fever (1)	Headache (1)	[60]
	CoV2 preS dTM	USCo	≥18	1/2	441 (378 vs. 63)	Pain (8), erythema (23), swelling (12), fever (11), malaise (31), and myalgia (25)	Headache (17)	[61]
	SCB-2019	Belgium, Brazil, Colombia, Philippines, and South Africa	≥18	3	30,128 (15,064 vs. 15,064)	DNP	DNP	[62]
	MVC-COV1901	China	≥20	2	3,854 (3,304 vs. 550)	None	None	[63]
	SOBERANA 02	Cuba	19–80	3	44,031 (29,356 vs. 14,675)	DNP	DNP	[64]
	Recombinant COVID-19 vaccine (Sf9 cells)	China	≥18	2	960 (800 vs. 160)	Redness (1) and swelling (1)	None	[65]
	Abdala	Cuba	19–80	2	726 (484 vs. 242)	None	None	[66]
	Nanocovax	Vietnam	≥18	2	560 (480 vs. 80)	Pain (DNP), redness (1), fatigue (DNP), and swelling (DNP)	None	[67]
	MF59-adjuvanted subunit vaccine	Australia	18–55	1	120 (96 vs. 24)	Injection site pain (1) and malaise (1)	None	[68]
	Recombinant fusion protein vaccine (V-01)	China	≥18	2	880 (720 vs. 160)	DNP	DNP	[69]
Virus-like particle	CoVLP	Argentina, Brazil, Canada, Mexico, UK, and US	18–86	3	24,076 (12,036 vs. 12,040)	None	None	[70]
DNA	INO-4800	US	≥18	2/3	399 (298 vs. 101)	Arthralgia (1)	None	[71]

UAE, the United Arab Emirates; UK, the United Kingdom; US, the United States; RK, the Republic of Kazakhstan; DNP, data not provided.

Table 3. Case reports of neurological AEs during mass vaccination campaigns

Vaccine	Neurological AEs	Reference
AZD1222	GBS	[73]
	CVST	[74]
	TM	[75]
Ad26.COV2.S	CVST	[76]
	TM	[77]
mRNA-1273	Bell's palsy	[78]
	CVT	[79]
	PTS	[80]
BNT162b2	Bell's palsy	[81]
	GBS	[82]
	CVT	[79]
	SFN	[83]
	PTS	[80]
	Delirium	[84]

GBS, Guillain-Barré syndrome; CVST, cerebral venous sinus thrombosis; TM, transverse myelitis; CVT, cerebral venous thrombosis; SFN, small fiber neuropathy; PTS, Parsonage-Turner syndrome.

splice donor sequences, especially SD506 and SD3614, which are the strongest predicted splice donor sites in the AZD1222 sequence [86]. This may be a cause of the ~3-fold lower incidence of thromboembolic side effects in the Ad26.COV2.S when compared to the AZD1222 vaccine. Thus, CVST should draw more attention of neurologists due to the disease site. However, it must be noted that even if vaccination does trigger cerebral venous thrombosis (CVT), the incidence after COVID-19 diagnosis was around 8-fold the incidence following an AZD1222 vaccine (39.0 per million people compared to 5.0 per million people) [87]. Moreover, headache is the most common symptom of CVST, which presents in 80–90% of cases [88]. It is probably caused by two main factors: the raised intracranial pressure and the local involvement of the pain-sensitive fibers of the dura mater by local inflammatory reaction, distension of the sinus wall, or leakage of blood on the surface of the brain [89]. In addition, the intracellular formation of the spike protein of SARS-CoV-2 or immune response triggered by that protein may also be involved in the pathophysiological mechanisms of headache after vaccination.

During the mass vaccination campaign, cases of transverse myelitis (TM) have been reported (Table 3). The strict temporal relationship between vaccination and TM, together with the absence of clues pointing to alternative diagnoses, makes vaccination to be considered as the potential trigger [90]. Moreover, the short interval between the onset of symptoms and the vaccination might indicate a nonspecific immunological mechanism of bystander activation. Nevertheless, as of 23 February 2022, more than 16 million doses of Ad26.COV2.S vaccine have been administered in the US, and only 34 cases of TM have been reported to VAERS. Considering that the annual incidence of TM is between 1.3 and 8 cases per million, the benefits of vaccination still seem to outweigh the associated risks.

RNA Vaccine

Cases of Bell's palsy after BNT162b2 or mRNA-1273 vaccination have been reported during mass vaccination campaigns (Table 3). In a letter, Cirillo and Doan [91] suggested that the relative risk of Bell's palsy was 1.5–3 times higher following COVID-19 mRNA vaccines than in the background population. Moreover, time of onset and outcome of Bell's palsy caused by the COVID-19 vaccine are similar to a previous mRNA rabies vaccine [92]. Thus, COVID-19 mRNA vaccine should be regarded as a risk factor for Bell's palsy. On the one hand, the combination of lipids and mRNA in vaccine could induce production of interferon proteins. Its potential mechanism has been further strengthened by some biological arguments. For example, interferon-alpha therapy caused the breakdown of tolerance to the myelin sheath and its native cell, and this is thought to play an important role in the pathogenesis of Bell's palsy [93]. On the other hand, mRNA vaccine seems to destroy the body's ability to prevent latent viruses from "waking up." Following BNT162b2 vaccination, 6 patients with underlying rheumatologic conditions developed herpes zoster [94] that is usually considered caused by the reactivation of varicella zoster virus (VZV) from sensory neurons. The possible explanation is that vaccination elicits a coordinated cellular and humoral adaptive immunity with a massive shift of naive CD8+ cells to spike-specific CD8+ T cell, making VZV-specific CD8+ cell unable to control VZV in a short period of time. Of note, the reactivation of VZV is one of the causes of Bell's palsy, and it would occur more frequently as the immune system ages. Thus, some people recommend high-risk patients (i.e., patients over 50 years of age) to receive the shingles vaccine prior to mRNA vaccination. This is an important point which deserves further discussion, since herpes zoster is frequently associated with permanent facial nerve dysfunction and severe disability es-

pecially for elderly patients even though it is a transient disease and has a very low mortality rate. Moreover, the present available treatments can only control the infection, change the severity and the duration of pain, and prevent post-herpetic neuralgia.

During the mass vaccination campaign, several individuals developed GBS within a few weeks of mRNA vaccination (Table 3). Unlike vaccines based on the adenovirus vector, the available evidence is insufficient to prove the association between the disease and mRNA vaccines. Although a study showed that the BNT162b2 vaccine may increase the risk, gastrointestinal infections known to induce GBS were also detected [95], suggesting that concurrent infectious triggers may be responsible for most cases.

The proportion of CVT was similar in the mRNA and ChAdOx1 nCoV-19 vaccine groups (4.1 per million people compared to 5.0 per million people) [87]. Nevertheless, there have been few reports of thrombocytopenia in the cases of CVT following mRNA vaccines, implying that the mechanism of vaccine-induced thrombosis is probably different between mRNA and adenovirus platform vaccines. Talotta [96] proposed that mRNA may bind to pattern recognition receptors, resulting in the activation of several pro-inflammatory cascades. Theoretically, this immune response may contribute as a trigger for thromboembolic events, but the exact pathophysiological mechanism and the relationship with headache remain to be further studied. In addition, although rare, a small number of cases of Parsonage-Turner syndrome (PTS), small fiber neuropathy, and delirium after mRNA vaccination have been described in the literature [80, 83, 84], and they are thought to be related to the vaccination. Given the post-vaccination PTS is often reported contralateral to the injected side, it is unlikely to be secondary to direct nerve injury from vaccination but may be caused by the mRNA vaccine-induced immune reaction.

Inactivated Vaccine, Virus-Like Particle Vaccine, and Protein Subunit Vaccine

Currently, clinical safety data of these three vaccines suggest that major local and systemic AEs were mild or moderate in severity with a short mean duration. Although a few serious AEs have occurred, most of them have been resolved. However, the data of some inactivated vaccines and protein subunit vaccines still have several obvious limitations such as the limited demographic diversity and small numbers of participants (Table 2).

Therefore, further data from larger sample sizes and longer duration are warranted to establish safety and obtain licensing before these vaccines can be administered to the general population.

Conclusion

COVID-19 is a major challenge to the human neurological health, as both the virus and the medications used to treat it could induce neurological symptoms. For one thing, SARS-CoV-2 can infect brain directly, which may be through hematogenous propagation and retrograde axonal transport except for the olfactory neuron pathway. For another, the virus can induce indirect neurotoxicity through immune-mediated pathogenesis and gastrointestinal infection. Although vaccination is currently the most effective way to protect the population from COVID-19, nevertheless, anti-vaccination advocates still hold that the data are not enough to justify the safety and effectiveness of vaccines and large-scale vaccination may result in some unprecedented issues. Admittedly, the data on some COVID-19 vaccines are incomplete when compared with traditional vaccines based on long-term studies with large samples. However, accumulating evidence has indicated that most AEs following vaccination are mild and self-limited. Only a few serious neurological AEs occurred, among which headache is most commonly reported and most can be relieved by rest. Moreover, other triggers instead of vaccination are more likely to lead to some serious neurological AEs (e.g., GBS after mRNA vaccination), and the incidence of several AEs (e.g., TM after Ad26.COV.S vaccination in the US) is similar to the annual incidence. On the contrary, the causal relationships between some vaccines and AEs (e.g., Bell's palsy after mRNA vaccination, and GBS and CVST after Ad26.COV2.S or AZD1222 vaccination) are considered plausible, and there is no doubt that these AEs should be sought, reported, and rigorously investigated further to facilitate ongoing safety evaluation. The clinicians should take these seriously in assessing the potential risks and benefits of vaccinations in a frail population. Nevertheless, given the rapid and extensive spread of COVID-19, the potential side effects of vaccination on nervous system should be compared with adverse COVID-19 outcomes rather than being considered alone. In other words, COVID-19 vaccination potentially has a dual effect on neurological disorders such as GBS and CVST. On the one hand, vaccination may directly increase the risk of neurological AEs through the above mechanisms. On the

other hand, it also could reduce the multiple risks by decreasing the risk of infection. Based on our review, the latter has a greater contribution. Thus, from the perspective of neurological health, it is obviously a wise option to be vaccinated instead of suffering from serious adverse symptoms of SARS-CoV-2 infection.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest in connection with this article.

Author Contributions

Fei Chen conceived the idea and drafted the manuscript; Pingdong Cao, Huimin Liu, and Dechen Cai searched the articles and extracted the data; all authors provided critical review and approved the final manuscript before submission.

References

1 World Health Organization. WHO Coronavirus disease (COVID19) dashboard. 2022. Available from: https://covid19.who.int/.

2 Mehta PR, Apap Mangion S, Benger M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination: a report of two UK cases. Brain Behav Immun. 2021 Jul;95:514–7.

3 Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020 Jun 1; 77(6):683–90.

4 Chou SH, Beghi E, Helbok R, Moro E, Sampson J, Altamirano V, et al. Global incidence of neurological manifestations among patients hospitalized with COVID-19: a report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. JAMA Netw Open. 2021 May 3;4(5):e2112131.

5 Zhang X, Wang F, Shen Y, Zhang X, Cen Y, Wang B, et al. Symptoms and health outcomes among survivors of COVID-19 infection 1 year after discharge from hospitals in Wuhan, China. JAMA Netw Open. 2021 Sep 1;4(9):e2127403.

6 Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord. 2021 Dec;22(4):803–15.

7 Gu WT, Zhou F, Xie WQ, Wang S, Yao H, Liu YT, et al. A potential impact of SARS-CoV-2 on pituitary glands and pituitary neuroendocrine tumors. Endocrine. 2021 May;72(2): 340–8.

8 Sato N, Watanabe K, Ohta K, Tanaka H. Acute transverse myelitis and acute motor axonal neuropathy developed after vaccinations against seasonal and 2009 A/H1N1 influenza. Intern Med. 2011;50(5):503–7.

9 Kelly H. Evidence for a causal association between oral polio vaccine and transverse myelitis: a case history and review of the literature. J Paediatr Child Health. 2006 Apr;42(4): 155–9.

10 Bir LS, Eşmeli FO, Cenikli U, Erdoğan C, Değirmenci E. Acute transverse myelitis at the conus medullaris level after rabies vaccination in a patient with Behçet's disease. J Spinal Cord Med. 2007;30(3):294–6.

11 Lim S, Park SM, Choi HS, Kim DK, Kim HB, Yang BG, et al. Transverse myelitis after measles and rubella vaccination. J Paediatr Child Health. 2004 Sep–Oct;40(9–10):583–4.

12 Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barre syndrome and the 1992–1993 and 1993–1994 influenza vaccines. N Engl J Med. 1998 Dec 17;339(25):1797–802.

13 Fransz DP, Schönhuth CP, Postma TJ, van Royen BJ. Parsonage-Turner syndrome following post-exposure prophylaxis. BMC Musculoskelet Disord. 2014 Aug 7;15:265.

14 Persson I, Granath F, Askling J, Ludvigsson JF, Olsson T, Feltelius N. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. J Intern Med. 2014 Feb;275(2):172–90.

15 Huynh W, Cordato DJ, Kehdi E, Masters LT, Dedousis C. Post-vaccination encephalomyelitis: literature review and illustrative case. J Clin Neurosci. 2008 Dec;15(12):1315–22.

16 Vrethem M, Malmgren K, Lindh J. A patient with both narcolepsy and multiple sclerosis in association with Pandemrix vaccination. J Neurol Sci. 2012 Oct 15;321(1–2):89–91.

17 Hernan MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurology. 2004 Sep 14;63(5):838–42.

18 Menge T, Cree B, Saleh A, Waterboer T, Berthele A, Kalluri SR, et al. Neuromyelitis optica following human papillomavirus vaccination. Neurology. 2012 Jul 17;79(3):285–7.

19 Bulfamante G, Chiumello D, Canevini MP, Priori A, Mazzanti M, Centanni S, et al. First ultrastructural autoptic findings of SARS-Cov-2 in olfactory pathways and brainstem. Minerva Anestesiol. 2020 Jun;86(6):678–9.

20 Remmelink M, De Mendonca R, D'Haene N, De Clercq S, Verocq C, Lebrun L, et al. Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. Crit Care. 2020 Aug 12;24(1):495.

21 Li YC, Zhang Y, Tan BH. What can cerebrospinal fluid testing and brain autopsies tell us about viral neuroinvasion of SARS-CoV-2. J Med Virol. 2021 Jul;93(7):4247–57.

22 Bryche B, St Albin A, Murri S, Lacote S, Pulido C, Ar Gouilh M, et al. Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. Brain Behav Immun. 2020 Oct;89:579–86.

23 Leist SR, Dinnon KH 3rd, Schafer A, Tse LV, Okuda K, Hou YJ, et al. A mouse-adapted SARS-CoV-2 induces acute lung injury and mortality in standard laboratory mice. Cell. 2020 Nov 12;183(4):1070–85.e12.

24 Zhang AJ, Lee AC, Chu H, Chan JF, Fan Z, Li C, et al. Severe acute respiratory syndrome Coronavirus 2 infects and damages the mature and immature olfactory sensory neurons of hamsters. Clin Infect Dis. 2021 Jul 15;73(2): e503–12.

25 Zheng J, Wong LR, Li K, Verma AK, Ortiz ME, Wohlford-Lenane C, et al. COVID-19 treatments and pathogenesis including anosmia in K18-hACE2 mice. Nature. 2021 Jan; 589(7843):603–7.

26 Butowt R, Meunier N, Bryche B, von Bartheld CS. The olfactory nerve is not a likely route to brain infection in COVID-19: a critical review of data from humans and animal models. Acta Neuropathol. 2021 Jun;141(6):809–22.

27 Ye Q, Zhou J, Yang G, Li R-T, He Q, Zhang Y, et al. SARS-CoV-2 infection causes transient olfactory dysfunction in mice. bioRxiv. 2020. Epub ahead of print.

28 de Melo GD, Lazarini F, Levallois S, Hautefort C, Michel V, Larrous F, et al. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. Sci Transl Med. 2021 Jun 2;13(596):eabf8396.

29 Schwob JE. Neural regeneration and the peripheral olfactory system. Anat Rec. 2002 Feb 15;269(1):33–49.

30 Scoppettuolo P, Borrelli S, Naeije G. Neurological involvement in SARS-CoV-2 infection: a clinical systematic review. Brain Behav Immun Health. 2020 May;5:100094.

31 Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Yingjie Qi RS, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. Natl Sci Rev. 2020;7(6):998–1002.

32 Yang YH, Huang YH, Chuang YH, Peng CM, Wang LC, Lin YT, et al. Autoantibodies against human epithelial cells and endothelial cells after severe acute respiratory syndrome (SARS)-associated coronavirus infection. J Med Virol. 2005 Sep;77(1):1–7.

33 Kim S, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, et al. Transneuronal propagation of pathologic alpha-synuclein from the gut to the brain models Parkinson's disease. Neuron. 2019 Aug 21;103(4):627–41. e7.

34 Shi Y, Li Z, Yang C, Liu C. The role of gut-brain axis in SARA-CoV-2 neuroinvasion: culprit or innocent bystander? Brain Behav Immun. 2021 May;94:476–7.

35 Chen F, Hao L, Zhu S, Yang X, Shi W, Zheng K, et al. Potential adverse effects of dexamethasone therapy on COVID-19 patients: review and recommendations. Infect Dis Ther. 2021 Dec;10(4):1907–31.

36 RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021 Feb 25; 384(8):693–704.

37 Vivithanaporn P, Asahchop EL, Acharjee S, Baker GB, Power C. HIV protease inhibitors disrupt astrocytic glutamate transporter function and neurobehavioral performance. AIDS. 2016 Feb 20;30(4):543–52.

38 von der Ahe D, Huehnchen P, Balkaya M, Peruzzaro S, Endres M, Boehmerle W. Suramin-induced neurotoxicity: preclinical models and neuroprotective strategies. Molecules. 2018 Feb 7;23(2):346.

39 Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. N Engl J Med. 2021 Dec 16; 385(25):2348–60.

40 Halperin SA, Ye L, MacKinnon-Cameron D, Smith B, Cahn PE, Ruiz-Palacios GM, et al. Final efficacy analysis, interim safety analysis, and immunogenicity of a single dose of recombinant novel coronavirus vaccine (adenovirus type 5 vector) in adults 18 years and older: an international, multicentre, randomised, double-blinded, placebo-controlled phase 3 trial. Lancet. 2022 Jan 15;399(10321): 237–48.

41 Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021 Feb 20;397(10275):671–81.

42 Hardt K, Vandebosch A, Sadoff J, Gars ML, Truyers C, Lowson D, et al. Efficacy and safety of a booster regimen of Ad26.COV2.S vaccine against Covid-19. medRxiv. 2022. Epub ahead of print.

43 Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021 Jun 10; 384(23):2187–201.

44 El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med. 2021 Nov 4;385(19):1774–85.

45 Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med. 2021 Nov 4;385(19):1761–73.

46 Kremsner PG, Ahuad Guerrero RA, Arana-Arri E, Aroca Martinez GJ, Bonten M, Chandler R, et al. Efficacy and safety of the CVnCoV SARS-CoV-2 mRNA vaccine candidate in ten countries in Europe and Latin America (HERALD): a randomised, observer-blinded, placebo-controlled, phase 2b/3 trial. Lancet Infect Dis. 2022 Mar;22(3):329–40.

47 Chen GL, Li XF, Dai XH, Li N, Cheng ML, Huang Z, et al. Safety and immunogenicity of the SARS-CoV-2 ARCoV mRNA vaccine in Chinese adults: a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Microbe. 2022 Mar;3(3):e193–202.

48 Palacios R, Batista AP, Albuquerque CSN, Patiño EG, do Prado Santos J, Tilli Reis Pessoa Conde M, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: the PROFISCOV study. 2021. Available from SSRN: https://ssrncom/abstract=3822780 http://dxdoiorg/102139/ssrn3822780.

49 Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021 Jul 17;398(10296):213–22.

50 Bueno SM, Abarca K, González PA, Gálvez NM, Soto JA, Duarte LF, et al. Interim report: safety and immunogenicity of an inactivated vaccine against SARS-CoV-2 in healthy chilean adults in a phase 3 clinical trial. medRxiv. 2021. Epub ahead of print.

51 Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA. 2021 Jul 6; 326(1):35–45.

52 Che Y, Liu X, Pu Y, Zhou M, Zhao Z, Jiang R, et al. Randomized, double-blinded and placebo-controlled phase II trial of an inactivated SARS-CoV-2 vaccine in healthy adults. Clin Infect Dis. 2021 Dec 6;73(11):e3949–55.

53 Khairullin B, Zakarya K, Orynbayev M, Abduraimov Y, Kassenov M, Sarsenbayeva G, et al. Efficacy and safety of an inactivated whole-virion vaccine against COVID-19, QazCovid-in®, in healthy adults: a multicentre, randomised, single-blind, placebo-controlled phase 3 clinical trial with a 6-month follow-up. 2022. Available at SSRN: https://ssrncom/abstract=4016484 http://dxdoiorg/102139/ssrn4016484.

54 Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a, double-blind, randomised, controlled phase 3 trial. medRxiv. 2021. Epub ahead of print.

55 Pan H, Liu J, Huang B, Li G, Chang X, Liu Y, et al. Immunogenicity and safety of a SARS-CoV-2 inactivated vaccine (KCONVAC) in healthy adults: two randomized, double-blind, and placebo-controlled phase 1/2 clinical trials. medRxiv. 2021. Epub ahead of print.

56 Pitisuttithum P, Luvira V, Lawpoolsri S, Muangnoicharoen S, Kamolratanakul S, Sivakorn C, et al. Safety and immunogenicity of an inactivated recombinant newcastle disease virus vaccine expressing SARS-CoV-2 spike: interim results of a randomised, placebo-controlled, phase 1/2 trial. medRxiv. 2021. Epub ahead of print.

57 Ishmukhametov AA, Siniugina AA, Yagovkina NV, Kuzubov VI, Zakharov KA, Volok VP, et al. Safety and immunogenicity of inactivated whole virion vaccine CoviVac against COVID-19: a multicenter, randomized, double-blind, placebo-controlled phase I/II clinical trial. medRxiv. 2022. Epub ahead of print.

58 Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med. 2021 Sep 23;385(13):1172–83.

59 Dunkle LM, Kotloff KL, Gay CL, Anez G, Adelglass JM, Barrat Hernandez AQ, et al. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. N Engl J Med. 2022 Feb 10;386(6):531–43.

60 Yang S, Li Y, Dai L, Wang J, He P, Li C, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis. 2021 Aug;21(8):1107–19.

61 Goepfert PA, Fu B, Chabanon AL, Bonaparte MI, Davis MG, Essink BJ, et al. Safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: interim results of a randomised, placebo-controlled, phase 1–2, dose-ranging study. Lancet Infect Dis. 2021 Sep;21(9):1257–70.

62 Bravo L, Smolenov I, Han HH, Li P, Hosain R, Rockhold F, et al. Efficacy of the adjuvanted subunit protein COVID-19 vaccine, SCB-2019: a phase 2 and 3 multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2022 Jan 29;399(10323):461–72.

63 Hsieh SM, Liu MC, Chen YH, Lee WS, Hwang SJ, Cheng SH, et al. Safety and immunogenicity of CpG 1018 and aluminium hydroxide-adjuvanted SARS-CoV-2 S-2P protein vaccine MVC-COV1901: interim results of a large-scale, double-blind, randomised, placebo-controlled phase 2 trial in Taiwan. Lancet Respir Med. 2021 Dec;9(12):1396–406.

64 Toledo-Romani ME, Garcia-Carmenate M, Silva CV, Baldoquin-Rodriguez W, Pérez MM, Gonzalez MCR, et al. Efficacy and safety of SOBERANA 02, a COVID-19 conjugate vaccine in heterologous three-dose combination. medRxiv. 2021. Epub ahead of print.

65 Meng FY, Gao F, Jia SY, Wu XH, Li JX, Guo XL, et al. Safety and immunogenicity of a recombinant COVID-19 vaccine (Sf9 cells) in healthy population aged 18 years or older: two single-center, randomised, double-blind, placebo-controlled, phase 1 and phase 2 trials. Signal Transduct Target Ther. 2021 Jul 15;6(1):271.

66 Hernández-Bernal F, Ricardo-Cobas MC, Martín-Bauta Y, Navarro-Rodríguez Z, Piñera-Martínez M, Quintana-Guerra J, et al. Safety, tolerability, and immunogenicity of a SARS-CoV-2 recombinant spike protein vaccine: a randomised, double-blind, placebo-controlled, phase 1-2 clinical trial (ABDALA Study). medRxiv. 2021. Epub ahead of print.

67 Nguyen TP, Do Q, Phan LT, Dinh DV, Khong H, Hoang LV, et al. Safety and immunogenicity of Nanocovax, a SARS-CoV-2 recombinant spike protein vaccine. medRxiv. 2021. Epub ahead of print.

68 Chappell KJ, Mordant FL, Li Z, Wijesundara DK, Ellenberg P, Lackenby JA, et al. Safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-CoV-2: a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Infect Dis. 2021 Oct;21(10):1383–94.

69 Shu YJ, He JF, Pei RJ, He P, Huang ZH, Chen SM, et al. Immunogenicity and safety of a recombinant fusion protein vaccine (V-01) against coronavirus disease 2019 in healthy adults: a randomized, double-blind, placebo-controlled, phase II trial. Chin Med J. 2021 Jul 22;134(16):1967–76.

70 Hager KJ, Marc GP, Gobeil P, Diaz RS, Heizer G, Llapur C, et al. Efficacy and safety of a plant-based virus-like particle vaccine for COVID-19 adjuvanted with AS03. medRxiv. 2022. Epub ahead of print.

71 Mammen MP Jr, Tebas P, Agnes J, Giffear M, Kraynyak KA, Blackwood E, et al. Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: a preliminary report of a randomized, blinded, placebo-controlled, phase 2 clinical trial in adults at high risk of viral exposure. medRxiv. 2021. Epub ahead of print.

72 Gobel CH, Heinze A, Karstedt S, Morscheck M, Tashiro L, Cirkel A, et al. Clinical characteristics of headache after vaccination against COVID-19 (coronavirus SARS-CoV-2) with the BNT162b2 mRNA vaccine: a multicentre observational cohort study. Brain Commun. 2021;3(3):fcab169.

73 Min YG, Ju W, Ha YE, Ban JJ, Lee SA, Sung JJ, et al. Sensory Guillain-Barre syndrome following the ChAdOx1 nCov-19 vaccine: report of two cases and review of literature. J Neuroimmunol. 2021 Aug 8;359:577691.

74 Krzywicka K, Heldner MR, Sanchez van Kammen M, van Haaps T, Hiltunen S, Silvis SM, et al. Post-SARS-CoV-2-vaccination cerebral venous sinus thrombosis: an analysis of cases notified to the European Medicines Agency. Eur J Neurol. 2021 Nov;28(11):3656–62.

75 Pagenkopf C, Südmeyer M. A case of longitudinally extensive transverse myelitis following vaccination against Covid-19. J Neuroimmunol. 2021 Sep 15;358:577606.

76 See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. JAMA. 2021 Jun 22;325(24):2448–56.

77 Tahir N, Koorapati G, Prasad S, Jeelani HM, Sherchan R, Shrestha J, et al. SARS-CoV-2 vaccination-induced transverse myelitis. Cureus. 2021 Jul;13(7):e16624.

78 Martin-Villares C, Vazquez-Feito A, Gonzalez-Gimeno MJ, de la Nogal-Fernandez B. Bell's palsy following a single dose of mRNA SARS-CoV-2 vaccine: a case report. J Neurol. 2022 Jan;269(1):47–8.

79 Abbattista M, Martinelli I, Peyvandi F. Comparison of adverse drug reactions among four COVID-19 vaccines in Europe using the EudraVigilance database: thrombosis at unusual sites. J Thromb Haemost. 2021 Oct;19(10):2554–8.

80 Queler SC, Towbin AJ, Milani C, Whang J, Sneag DB. Parsonage-Turner syndrome following COVID-19 vaccination: MR neurography. Radiology. 2022 Jan;302(1):84–7.

81 Colella G, Orlandi M, Cirillo N. Bell's palsy following COVID-19 vaccination. J Neurol. 2021 Oct;268(10):3589–91.

82 Razok A, Shams A, Almeer A, Zahid M. Post-COVID-19 vaccine Guillain-Barré syndrome; first reported case from Qatar. Authorea. 2021 Jul;67:102540.

83 Waheed W, Carey ME, Tandan SR, Tandan R. Post COVID-19 vaccine small fiber neuropathy. Muscle Nerve. 2021 Jul;64(1):E1–2.

84 Zavala-Jonguitud LF, Perez-Garcia CC. Delirium triggered by COVID-19 vaccine in an elderly patient. Geriatr Gerontol Int. 2021 Jun;21(6):540.

85 Allen CM, Ramsamy S, Tarr AW, Tighe PJ, Irving WL, Tanasescu R, et al. Guillain-Barre syndrome variant occurring after SARS-CoV-2 vaccination. Ann Neurol. 2021 Aug;90(2):315–8.

86 Kowarz E, Krutzke L, Kulp M, Streb P, Larghero P, Reis J, et al. Vaccine-induced COVID-19 mimicry syndrome. Elife. 2022 Jan 27;11:e74974.

87 Taquet M, Husain M, Geddes JR, Luciano S, Harrison PJ. Cerebral venous thrombosis and portal vein thrombosis: a retrospective cohort study of 537,913 COVID-19 cases. EClinicalMedicine. 2021 Sep;39:101061.

88 Singh RJ, Saini J, Varadharajan S, Kulkarni GB, Veerendrakumar M. Headache in cerebral venous sinus thrombosis revisited: exploring the role of vascular congestion and cortical vein thrombosis. Cephalalgia. 2018 Mar;38(3):503–10.

89 Agostoni E. Headache in cerebral venous thrombosis. Neurol Sci. 2004 Oct;25 Suppl 3:S206–10.

90 Vegezzi E, Ravaglia S, Buongarzone G, Bini P, Diamanti L, Gastaldi M, et al. Acute myelitis and ChAdOx1 nCoV-19 vaccine: casual or causal association? J Neuroimmunol. 2021 Jul 31;359:577686.

91 Cirillo N, Doan R. Bell's palsy and SARS-CoV-2 vaccines-an unfolding story. Lancet Infect Dis. 2021 Sep;21(9):1210–1.

92 Soeiro T, Salvo F, Pariente A, Grandvuillemin A, Jonville-Béra AP, Micallef J. Type I interferons as the potential mechanism linking mRNA COVID-19 vaccines to Bell's palsy. Therapie. 2021 Jul–Aug;76(4):365–7.

93 Greco A, Gallo A, Fusconi M, Marinelli C, Macri GF, de Vincentiis M. Bell's palsy and autoimmunity. Autoimmun Rev. 2012 Dec;12(2):323–8.

94 Furer V, Zisman D, Kibari A, Rimar D, Paran Y, Elkayam O. Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. Rheumatology. 2021 Oct 9;60:SI90–5.

95 Garcia-Grimshaw M, Michel-Chavez A, Vera-Zertuche JM, Galnares-Olalde JA, Hernandez-Vanegas LE, Figueroa-Cucurachi M, et al. Guillain-Barre syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine. Clin Immunol. 2021 Sep;230:108818.

96 Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases". Clin Immunol. 2021 Mar;224:108665.