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

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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, COVID-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.

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,
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-

| 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.
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 involvement 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-
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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 Th 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
| 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), diarhera (7), vomiting (1), generalized muscle aches (65), redness (4), swelling (3), and pain (49) | Headache (85)                                                                                                          | [40]      |
| 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), diarhera (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 | 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 | None | [49]     |
|       | Chile   | ≥18      | 3   | 434 (270 vs. 164) | None | 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       | China   | 18–59    | 2   | 750 (600 vs. 150) | None | None | None | [52]     |
|                  | vaccine (vero cells) |               |     |     |                           |                    |                                            |           |
| QazCovid-in®     | RK      | ≥18      | 3   | 3,000 (2,400 vs. 600) | None | None | None | [53]     |
| BBV152           | India   | 18–98    | 3   | 25,798 (12,899 vs. 12,899) | DNP | DNP | DNP | [54]     |
| KCONVAC          | China   | 18–59    | 2   | 500 (400 vs. 100) | None | None | None | [55]     |
| NDV-HXP-S        | Thailand| 18–59    | 1/2 | 210 (175 vs. 35) | None | None | None | [56]     |
| CoviVac          | Russia  | 18–60    | 1/2 | 398 (298 vs. 100) | None | 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) |
|                  |                           | 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) |
|                  | 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) |
|                  | 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) |
|                  | 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.
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 thrombembolic 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.

### 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.
especially 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.

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**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.
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