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REVIEW ARTICLE

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The potential neurological effect of the COVID-19 vaccines: A review

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Abstract

The coronavirus disease 2019 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic with people infected in almost all countries. The most efficient solution to end this pandemic is a safe and efficient vaccine. Classic platforms are used to develop vaccines including live-attenuated vaccine, inactivated vaccine, protein subunit vaccine, and viral vector. Nucleic acid vaccine uses next-generation platforms for their development. Vaccines are now rushing to the market. Eleven candidates are in advance development. These comprise inactivated vaccines, viral vector vaccine, nucleic acid vaccine, and the protein subunit vaccine platform, which are now quite advanced in trials in various geographic and ethnic populations. The reported severe adverse effects raised the worries about their safety. It becomes critical to know whether these vaccines will cause neurologic disorders like previously recognized vaccine-related demyelinating diseases, fever-induced seizure, and other possible deficits. We reviewed the most promising COVID-2 vaccines with a particular interest in mechanism(s) and adverse effect(s). We exemplify potential neurological problems these vaccines could cause by looking at previous studies. The current evidence indicated a minor risk of the acute neurological disorders after the application. The observation of the long-time effect is still needed.

KEYWORDS
adverse effect, demyelinating disease, safety, SARS-CoV-2

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 and caused the coronavirus disease 2019 (COVID-19), which is now pandemic. To date, the COVID-19 has infected over one million people worldwide, and more than two million deaths were reported. The secondary wave of the pandemic was just about to left. The most promising solution remains to be an efficient vaccine.

Lu Lu and Weixi Xiong contributed equally.

The development of the vaccines starts as soon as the virus genome was published in early January.[1] The most significant difference in developing a COVID-19 vaccine is the wide range of technology platforms used.[2] Some of these platforms, however, have not been widely used previously.[3] The Pfizer-BioNTech vaccine has become the first licensed product. Vaccines against coronaviruses have not been previously licensed in humans.[4] A frequently asked question is whether the speed of development may compromise the vaccine's safety and efficiency.

Research suggests that the willingness of people getting immunization for COVID varies from 55% to 90%.[5-7] Over the past decades, vaccine hesitancy has steadily grown, partly due to fear of side effects arising from vaccination. Some reports have shown the neurologic side effects after immunization, mainly demyelinating diseases (Table 1). Some studies also suggest that post-vaccination demyelination is most likely acting as triggers of clinical disease expression in individuals who already have an underlying disease process.[8] Another frequently reported adverse effect is acute systematic seizures. Some previously reported vaccine-induced seizures were reported in Dravet syndrome, in which it seems that vaccination-induced fever acts as a seizures trigger.[9]

Currently, a number of COVID-19 vaccines have been launching to the market, and the others are still in phase 3 clinical trials. Different techniques and mechanism are in use to develop them. Given the speed of this development and issuing, concerns exist. It becomes increasingly vital to emphasize the safety of the coming vaccination options in neurological disorders.

We systematically reviewed the released information of the 11 vaccine candidates entered phase 3 trials announced by the world health organization by November 2011.[10] None of them had finished all the phase 3 endpoints per protocol by February 2021.[11] We also discussed the mechanism and neurological adverse effects reported in the four vaccine platforms in which they are developed. We aim to clarify the potential neurological effects these vaccines may have based on previous experience.

2 | METHOD

2.1 | Search strategy

The review was designed based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol.[12] We searched systematically in PubMed and medRxiv using the keywords "COVID-19" or "SARS-CoV-2" and "vaccination" or "vaccine," to identify all studies from 1 January 2020, up to 28 February 2021. We also searched systematically in Google using the keywords "COVID-19" or "SARS-CoV-2," "vaccination" or "vaccine" and "adverse effect," to identify the official statement from the manufactures of the vaccine candidates and the drug authorities.

2.2 | Study selection

We excluded reviews, editorials, letters, and animal studies. Those in-human phase 3 trial cited in the draft landscape of WHO were included. The inclusion criteria were as follows: (1) Participants were healthy adults older than 18 years without previous history of COVID-19 infection or previous underlying medical history; (2) randomized, placebo-controlled design, and (3) safety and efficiency were evaluated.

The selected studies were then independently reviewed by three co-authors (LL, WX, and JM) for adverse effect with a particular interest in neurological issues.

2.3 | Data synthesis

The frequency of neurological adverse events and the differences in efficiency parameters between vaccine candidates and their control were pooled and stratified.

TABLE 1 Frequently reported Neurological adverse effects

Adverse effect		Vaccines
Demyelination disease	Multiple sclerosis (MS) Acute disseminated encephalomyelitis (ADEM) Transverse myelitis Optic neuritis	Hepatitis B vaccine[50] Human papillomavirus vaccine[51] Influenza vaccine Rabies vaccine[52] Yellow fever vaccine[53]
Guillain-Barré syndrome (GBS)		Influenza vaccine [54] Oral polio vaccine Tetanus vaccines[55]
Encephalopathy		Whole-cell pertussis vaccine[56] Influenza Vaccine
Seizure		Diphtheria, tetanus toxoids and whole-cell pertussis vaccine (DTP) Measles, mumps, and rubella vaccine (MMR) [9]
Autism		MMR[57]a

[a]The original manuscript had been withdrawn.

2.4 | Results

We initially identified 505,214 articles in PubMed and 11693 in medRxiv. Forty-eight was selected for detailed reviewing. No major or significant neurological adverse effect was reported. Data on neurological adverse effects reported in COVID-19 vaccine candidates are shown in Table 2. Due to the limitation of reliable forthcoming evidence, we transformed this into a narrative review.

3 | DISCUSSION

Previous reports[28] on the development of severe acute respiratory syndrome coronavirus (SARS-CoV)vaccine and on middle east respiratory syndrome coronavirus (MERS-CoV) vaccine suggested that the spike protein, primarily its receptor-binding domain (RBD), could serve as an antigenic target in developing a vaccine against SARS-CoV-2.[29]

The vaccine's goal is to produce antibodies that can neutralize pathogens or flag them for destruction by the immune system. Despite different platforms used, modern vaccines share components with risk of neurological adverse effects (shown in Table 3). Different technological platforms have been used to introduce the selected antigen to the immune system. Eleven candidate vaccines are undergoing large-scale development programs worldwide using four different platforms. The varied components in those candidates and their mode of action raised a range of potential adverse effects.

3.1 | Inactivated vaccine

The inactivated vaccine is one of the most traditional platforms. Chemicals or heat renders the virus uninfectious. This platform's safety and efficiency have been previously proved in vaccines against the influenza virus. The non-infective nature of the attenuated virus requires enhancing immunogenicity and stimulation of cellular immunity using adjuvants.[30] The degree to which inactivated vaccines are tolerated depends on the purification techniques used to remove other proteins associated with the infectious agent and the nature of the adjuvants.[31]

A febrile reaction after inactivated vaccines is a common adverse reaction. The mechanisms responsible for the febrile response remain unclear. One hypothesis is that high inflammatory cytokines are associated with more robust immune responses and a febrile reaction.[32] But no febrile seizure was reported so far in the COVID-19 trials. Another concern is about the associations between vaccines and autoimmune disorders, including Guillain-Barré syndrome (GBS), multiple sclerosis (MS), and other demyelinating disorders. A recent systematic review about the association between different inactivated vaccines (HPV, influenza, tetanus, Bacillus Calmette-Guérin (BCG), polio, or diphtheria) and central demyelinating disorders, however, found no relationship between these vaccines and MS.[33] Similarly, another review of e vaccine-associated neurological adverse events found no direct evidence of increased risk of GBS and anti-NMDA receptor encephalitis after vaccination.[34]

Adjuvants are used in such vaccines. They raise concerns about the potential adverse effect they could have, particularly at the injection site and the mediators' responses and inflammatory influx. Most candidates in this platform use alum adjuvant. To date, no related severe adverse effect (SAE) has been reported.

Immunization stress–related response (ISRR) was also reported in this platform.[35] In some cases, the clinical manifestations of ISRR include psychogenic non-epileptic seizures (PNES). The video electroencephalograph monitoring would be valuable in diagnosed. PNES and other symptoms of ISRR can be easily spread by sight, sound, or oral communication to others. The profound psychological distress and the circumstantial stress during the COVID-19 pandemic could be a potential trigger of PNES.[36]

According to the WHO, ten clinical evaluation candidates use the inactivated virus, and seven are in the advanced phase 3 trial. A "serious adverse event" led the Brazilian drug administration authority to halt the Sinovac vaccine clinical trials. Once it was established that the participant committed suicide, the Brazilian authority restarted it.

3.2 | Viral vector vaccine

Viral vector vaccines consist of a recombinant virus, in which genes encoding viral antigen(s) have been cloned using recombinant DNA techniques. In the four candidates in this category, the vaccine will enter cells and produce the antigen without new virus particles formed. This recombinant adenovirus or adeno-based virus vectors are widely used because of their high transduction efficiency, high level of transgene expression, and a broad range of viral tropism.[37]

The viral vector platform had shown a precise gene delivery into the host cell with a vigorous immune response. It also avoids the handling of infectious particles. The vector prior exposure could reduce the efficacy. There are concerns about cancer inducement due to the integration of the viral genome into host genome.

This platform was used in the vesicular stomatitis virus-based Ervebo vaccine against Ebola virus,[38] where no serious safety signals were identified.

The primary concern in this platform is raised from the vaccine ChAdOx1 nCoV-19. The same technology had proved successful in developing the MERS vaccine, where no severe adverse events were reported by 12 months. One serious adverse event was reported in the study but was considered not related to ChAdOx1 MERS.[39,40] The ChAdOx1 nCoV-19 clinical trial paused following a case of transverse myelitis(TM). The global clinical trials resumed after the confirmation of MS in the volunteer.[41] According to the interim analysis of their phase 3 trial,[17] there are 3 cases of TM, which was found among 11 636 participants included. One case is considered to be an idiopathic, short segment, and spinal cord demyelination, which is possibly related to vaccination. The other two were likely to be pre-existing or irrelevant. All four deaths were considered unrelated

TABLE 2 Landscape of the 11 COVID-19 vaccine candidates

Vaccine platform	Candidate	Developer	Number of doses	Outcome published in Humans	Published sample size	Phase 3 trial Sample size	Severe adverse effect	Neurological adverse effect
Inactivated	CoronaVac	Sinovac	2	Phase 1/2 in The Lancet Infectious Diseases[13]	743 (143 + 600)	13,060 in Brazil; 13000 in Turkey; 1620 in Indonesia	Phase 1: one case of urticaria 48 h after the first dose of in the 6 μg group in the days 0 and 14 vaccination cohort	None
Inactivated	No name announced	Wuhan Institute of Biological Products/ Sinopharm	2	Phase 1 and 2 in JAMA[14]	320 (96 + 224)	15,000 in UAE[a]; 600 in Morocco;	Phase 1: one case with swelling and pain of left knee joint and subcutaneous hematoma and another case acute appendicitis in high dose group Phase 2: one case of fever (39.0°), another case of skin laceration from left eyebrow arch to hair source, multiple skin contusion at nasal back.	None
Inactivated	BBIBP-CorV	Beijing Institute of Biological Products/ Sinopharm	2	Phase 1/2 in The Lancet Infectious Diseases[15]	640 (192 + 448)	15,000 in UAE[a]; 3000 in Argentine	Phase 2: One placebo recipient in the 4 μg days 0 and 21 group reported grade 3 fever,	None
Inactivated	Covaxin	Bharat Biotech	2	Bharat Biotech statement.	1100	26,000 in India	NA	NA
Non-Replicating Viral Vector	AZD1222	University of Oxford/ AstraZeneca	2	phase 1/2 in the Lancet[16] phase 3 in the Lancet[17]	1077 + 11,636	40,051	One hemolytic anemia case in the controlled vaccine (a meningococcal conjugate vaccine); * one death case in Brazil, phase 3 trial;	Cases of transverse myelitis were reported in phase 3 trail, 2 of them was considered irrelevant.

(Continues)

TABLE 2 (Continued)

Vaccine platform	Candidate	Developer	Number of doses	Outcome published in Humans	Published sample size	Phase 3 trial Sample size	Severe adverse effect	Neurological adverse effect
Non-Replicating Viral Vector	Ad5-nCoV	CanSino Biological Inc./Beijing Institute of Biotechnology	1	phase 1 and phase 2 in the Lancet[18]	616 (108 + 508)	500 in Russia; 40,000 in Pakistan, Saudi Arabia, and Mexico	Phase 1: Nine participants (two [6%] in the low dose group, two [6%] in the middle dose group, and five [14%] in the high dose group) had an episode of severe fever. One (3%) from the high dose group reported severe fever along with severe symptoms of fatigue, dyspnea, and muscle pain. One participant in the high dose group reported severe fatigue and joint pain.	None
Non-Replicating Viral Vector	Gam-COVID-Vac (Sputnik V)	Gamaleya Research Institute	2	Phase 1/2 in the Lancet[19] Phase 3 in the Lancet[20]	76 + 21,977	40,000 in Russia	Few serious adverse events, data not be published yet.	Data not be published yet
Non-Replicating Viral Vector	JNJ–78436735 (formerly Ad26.COV2.S)	Janssen Pharmaceutical Companies	1/2	Phase 1/2a data in the pre-print server MedRxiv[21]b	796 (402 + 394)	90,000	3 cases (0.8%) in cohort 1a (aged 18 to) and one in cohort 3(older than X) had grade 3 local adverse effect; 41 cases(10.9%) in cohort 1a, 5 cases(20%) in cohort 1b (aged 18 to 65) and 3 in cohort 3(older than 65) had grade 3 systemic adverse effect	None

(Continues)

TABLE 2 (Continued)

Vaccine platform	Candidate	Developer	Number of doses	Outcome published in Humans	Published sample size	Phase 3 trial Sample size	Severe adverse effect	Neurological adverse effect
Protein Subunit	NVX-CoV2373	Novava	2	phase 1 data in The New England Journal of Medicine[22]	131	10,000 in the UK	First injection: Two participants (2%), one each in groups D (received 25-μg doses of rSARS-CoV−2 plus Matrix-M1, including three sentinels)and E(received 25-μg doses of rSARS-CoV−2 plus Matrix-M1, including three sentinels), had severe adverse events (headache, fatigue, and malaise); Second injection: One participant, in group D, had a severe local event (tenderness), and eight participants, one or two participants in each group, had severe systemic events	None
RNA	mRNA−1273	Moderna/NIAID	2	Phase 1 data in the New England Journal of Medicine (adult[23]/ older adult[24]) Phase 3 data in New England Journal of Medicine[25]	45 + 30,420	30,000	One case of transient urticaria related to the first vaccination. Three with severe event(s) not specified	None
RNA	BNT162	BioNTech/Fosun Pharma/Pfizer	2	phase 1 data in the New England Journal of Medicine[26] the phase 2/3 data in the New England Journal of Medicine[27]	332 + 43,448	43,998	None	None

[a]These two trials shared a same phase 3 protocol; [b]Posted in the pre-print site MedRxiv

TABLE 3 The potential responsive components of vaccine

Main Components	Types
Antigen: The designed foreign material that can induce the immune response of a specific pathogen one aims to immunize against. There are various types of antigen in different vaccine platforms.[58]	*Live-attenuated vaccine: weakened form of pathogens capable of replication, but not causing illness.* *Inactivated vaccine: killed form of pathogens incapable of replication or infection.* *Viral vector vaccine: The gene encoding the antigen on a repurposed virus vector* *Nucleic acid vaccine: capsuled DNA or RNA encoding the antigen.*
Adjuvant: The stimulatory agent designed to emphases immune response in certain antigen type such as inactivated and subunit vaccine. A key adjuvant function is overcoming the poor immunogenicity of these vaccines by improving pathogen recognition and eliciting a response similar to the natural innate immune response.[59]	
Delivery system	*Viral vector:a repurposed mammalian viruses engineered to deliver a gene encoding the antigen* *Nanoparticles: nanoscale assemblies of synthetic materials engineered to present a subunit vaccine or deliver a nucleic acid encoding the antigen*

to the vaccine (caused by road traffic accident, blunt force trauma, homicide, and fungal pneumonia.)

The other promising candidate in this platform, Janssen Ad26.COV2.S Vaccine, also released its safety data through the Food and Drug Administration (FDA) briefing document. Among the seven serious adverse events (SAEs) found in the vaccine group, there were one case of GBS and one facial paralysis. Both cases were thought to have insufficient data to determine a causal relationship to vaccination.[42]

3.3 | Protein subunit vaccine

A subunit vaccine is based on the synthetic peptides or recombinant antigenic proteins. It is composed of at least one type of viral antigen produced in heterologous expression systems.[43]

The subunit vaccine was considered to be safer because its components only contain recombinant proteins or synthetic peptides, without the involvement of infectious viruses. The S Protein and its antigenic fragments are the prime targets for the institution of the subunit vaccine.[44] Since the subunit vaccine exhibits low immunogenicity, they require additional support of an adjuvant to potentiate the immune responses.

The only candidate from this section in phase 3 was NVX-CoV2373. It was composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant.[22] Matrix-M1 is a saponin-based adjuvant composed of Quillaja saponins, cholesterol, and phospholipid. Researches showed that therapeutic doses resulted in a local transient immune response with recruitment and activation of central immune cells to dLNs. This adjuvant has been used in the vaccine development of influenza virus, respiratory syncytial virus, and Ebola, but none has yet been licensed.[45] The long-term effect in human needs further evidence to confirm.

According to the published data from phase 1 and 1/2 trial of NVX-CoV2373, no neurological adverse effect was noted. It reported a patient with transient fever, while the most noted severe systemic events were joint pain and fatigue.

3.4 | Nucleic acid vaccine

Nucleic acid–based vaccines consist of DNA or mRNA and can be adapted quickly when new viruses emerge. The mRNA works by introducing an mRNA sequence that is coded for the S protein or RBD. Once interacting with the host's cells, it produces the specific antigen outside the cell surface to activate the immune system.

Most current research is into RNA vaccines for infectious diseases and cancer, for which there are several early-stage clinical trials. Compared with traditional vaccines, mRNA vaccines are safer. They are non-infectious as they do not contain pathogen particles or inactivated pathogen. RNA does not integrate itself into the host genome, and the RNA strand in the vaccine is degraded once the protein is made. Since mRNA is not very stable, these constructs include modified nucleosides to prevent degradation. A carrier molecule, such as lipid nanoparticles, is needed to enter the mRNA into cells. The doubt rises in these carriers, considering about 2% of the people had a severe fever and other transient adverse effect at the local infection site.[46] From the limited data available, it is clear that further understanding of adverse effect in this platform is required. There are concerns of long-term post-vaccination inflammation or autoimmune reaction behind the robust reactogenicity of it.

Comirnaty (BNT162b2) developed by Pfizer and BioNTech was the first licensed COVID-19 vaccine. The US FDA released their phase 3 data.[47] A total of 37796 participants were enrolled, of whom 18555 completed the two doses schedule. Their published phase 2/3 data[27] involve 43,448 participants received injection. No neurologic adverse event was noted in the vaccine group, and one of the four deaths in the placebo group was caused by hemorrhagic stroke.

In the FDA published fact sheet[48] of the other mRNA vaccine, mRNA-1273 developed by Moderna, the efficiency was calculated as 94.1% among 14,134 participants in vaccine group. The severe adverse events were reported by 1.0% of the participants in both vaccine group and placebo group. There was a case of Bell's palsy reported 32 days after the vaccine. This case was not noted in the published phase 3 data.[25]

4 | CONCLUSION

Only one among the 11 candidates in phase 3 stage has released the data in large-scale population. Preliminary results suggest that neurologic adverse effect is rare. Cases of demyelinating disease were reported in the viral vector vaccine. Fever was one of the most frequent effects on all platforms, particularly in the mRNA platform. It could lower the seizure threshold, as the international league against epilepsy warns.[49] Whether the vaccine could cause or trigger neurological disorders or incidentally lead to them need long-time monitoring—a cautious optimism toward the vaccine's safety in terms of neurological effect is appropriate.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest in relation to this work.

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