Neurologic Complications With Vaccines
What We Know, What We Don’t, and What We Should Do

Avindra Nath, MD

Abstract

Over the previous half century, vaccines have shaped human life by eradicating or nearly eradicating infections that were once a major cause of morbidity and mortality. The number of infections for which vaccines are now available has steadily increased. The types of vaccines have evolved over the years from crude extracts to more refined messenger RNA or protein-based vaccines. With these well-defined manufacturing processes, the safety profile has also improved. Despite such measures, vaccines are not without side effects, including those that affect the nervous system. Numerous case reports and case series point to these possibilities. These issues have gathered much attention during the current mass vaccination against severe acute respiratory syndrome coronavirus 2 and have resulted in some members of the public raising concerns about vaccine safety. The vaccine manufacturers have legal protection against vaccine side effects; however, there are active and passive surveillance programs put in place by the Center for Disease Control and Prevention, the US Food and Drug Administration, the World Health Organization, and the European Union. Action is needed that brings together manufacturers, healthcare agencies, clinical and bench scientists, and legislators on a global platform to investigate vaccine-related neurologic adverse events and develop ways to prevent and treat them.

Introduction

Infections have shaped the evolution of humans on this planet. Waves of infections commonly termed the "plague" wiped out large populations across the globe, and the remaining individuals repopulated the planet. Some humanoid species and human civilizations became extinct likely due to these infections. Our ability to control infections with the use of antimicrobial agents and vaccines has increased life expectancy, dramatically decreased morbidity and mortality from infections, and contributed to the development of modern society.1 Because safe and effective treatments for many pathogens are not available and infections can cause loss of life or significant lasting damage, the best measures against infections are vaccines. The goal of vaccination is the generation of long-lasting and protective immunity against pathogens. Vaccines have successfully eradicated smallpox, nearly eradicated polio,2,3 and significantly reduced many other devastating childhood diseases such as measles, rubella, and mumps. Many of the infections that are now preventable by vaccines are known to have severe neurologic manifestations (Table 1). These pathogens can cause an encephalitis resulting in seizures, alteration in behavior and personality, loss of cognitive abilities, and paralysis. Some infections such as varicella zoster and tetanus can cause excruciating pain. The culmination of these manifestations can be death or permanent disability.4 Although these infections are preventable by vaccinations, they can also spread rapidly among the unvaccinated and those who are immunocompromised. For these reasons, these infections are the most feared.

The goal of vaccination is the generation of long-lasting and protective immunity against pathogens known as immunologic memory. Once immunologic memory is established, the
Pathogen is often eliminated before it can even cause signs or symptoms. The process of making vaccines has evolved over the years. Through major technological advancements, vaccines are now made from either purified virus or its components, that is, proteins, peptides, or RNA. Each type of vaccine carries its own advantages and unique risks. For example, live attenuated vaccines while highly effective have the potential to cause disease in immunocompromised individuals and reversion to a virulent form by back sequence alterations or recombination with the wild-type strains. Hence, these vaccines need to be replaced by those that incorporate more recent developments in vaccine technology. Inactivated or killed vaccines use chemicals to cross-link the proteins and irradiation to inactivate the viral genome. Subunit and conjugate vaccines contain only a small part of the pathogens they protect against. They often have weak potency and require the use of adjuvants to drive a strong immune response. More recently, adenov-associated viral vectors have been used to incorporate the genes of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for immunization. Messenger RNA (mRNA)-based vaccines are currently in use for SARS-CoV-2. These vaccines use the cells’ own machinery to produce proteins. Protein production by the host cells mimics natural infection. These vaccines do not produce the entire virus, just the spike protein that is on the surface of the virus. The mRNA is packaged in lipid nanoparticles for efficient delivery to cells. The major advantage is the rapidity with which large amounts can be produced, distributed, and administered.

Thus, vaccines are manufactured in a variety of manners and may have adjuvants, may be formulated in lipid particles, or contain other components. The process of manufacturing also varies across vaccine types. Some vaccines are grown in eggs and others in cells in tissue culture or culture medium, which may also introduce contaminants or allergens. All these factors must be considered when studying the side effects of vaccinations. Of importance, some components of the vaccines are proprietary, which makes it difficult for anyone other than the manufacturers to study their effects.

### Table 1 Major Neurologic Manifestations of Infections for Which Vaccinations Are Available

<table>
<thead>
<tr>
<th>Infection</th>
<th>Neurologic manifestations</th>
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<tbody>
<tr>
<td>Smallpox/monkeypox</td>
<td>Acute disseminated encephalomyelitis, transverse myelitis, neuropathy</td>
</tr>
<tr>
<td>Measles</td>
<td>Acute encephalitis or subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Mumps</td>
<td>Acute encephalitis, meningitis, sensorineural deafness</td>
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<tr>
<td>Rubella</td>
<td>Congenital malformations; encephalitis</td>
</tr>
<tr>
<td>Influenza</td>
<td>Acute encephalitis; parkinsonism</td>
</tr>
<tr>
<td>Varicella zoster</td>
<td>Shingles; neuralgia, polyradiculitis, myelitis, encephalitis, and vasculopathy</td>
</tr>
<tr>
<td>Japanese encephalitis virus</td>
<td>Encephalitis, meningitis, myelitis</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>Encephalitis, myelitis</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Cerebrovascular disease; anosmia; long-COVID</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Tetany/severe spasms</td>
</tr>
<tr>
<td>Rabies</td>
<td>Paralysis; encephalitis</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Hemophilus influenza</td>
<td>Meningoencephalitis</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>Meningoencephalitis</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Meningitis, brain abscess, vasculopathy</td>
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</table>

Abbreviations: COVID = coronavirus disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Challenges in Determining Neurologic Complications of Vaccines

The published literature has a large list of case reports and case series with a wide variety of neurologic manifestations attributed to vaccines. While most side effects of vaccines are benign and transient, such as headache or fatigue, more serious side effects, including devastating neurologic complications, may occur. The Vaccine Adverse Event Reporting System (VAERS) database provides a long list of neurologic complications associated with all types of vaccines. As discussed further, the accuracy of the database is questionable; hence, determining the exact cause of the manifestations listed in the database has been challenging. The same dataset reveals that serious neurologic complications after vaccine administration across all vaccine types are extremely rare. Nonetheless, neurologic manifestations that are potentially attributed to vaccines include immune-mediated syndromes, major categories of which include the Guillain-Barre syndrome, small fiber neuropathies, transverse myelitis, and acute disseminated encephalomyelitis. Milder complications may have predominantly subjective symptoms, which can be challenging to document. For example, our group reported cases of peripheral neuropathies temporally associated with the SARS-CoV-2 vaccines. Many patients had subjective symptoms that were dismissed. Diagnosis required skin biopsies and/or autonomic testing, procedures that are only available in specialized centers. This poses challenges in diagnosing these conditions at a global level. There has been concern that vaccines can also mask an underlying neurologic condition such as multiple sclerosis and other immune-mediated conditions; however, several studies suggest that the risk is very low.

It is possible to raise concern about cause and effect when a rare manifestation occurs soon after an exposure to an agent even if a small population is affected and if the background rate of such a manifestation is rare in the unvaccinated population. An example might be the development of cerebral venous thrombosis with the Astra Zeneca Vaccine for SARS-CoV-2. The longer the interval between the administration of the agent and the clinical manifestation, the harder it is to make the association. Similarly, if the clinical manifestations are common, such as headaches, which can be seen with other common illnesses, determining causation requires large epidemiologic studies with proper matched controls. A similar challenge occurs in attributing rare complications such as peripheral neuropathies, tinnitus, and strokes, when the relative prevalence of these illnesses is higher in the unvaccinated population. An example of this complexity is the suggested association of Pandemrix, an AS03-adjuvanted monovalent pandemic H1N1 influenza vaccine, and pediatric narcolepsy. In Finland, there was an increase in the cases of pediatric narcolepsy in 2010, the year after the Pandemrix vaccine was used in Europe. Of a total of 54 cases of pediatric narcolepsy in the country, 50 cases had received the Pandemrix vaccine between 0 and 242 days before disease onset. 34 children had gene sequencing, and all carried the risk allele (DQB1*0602/DRB1*15) for narcolepsy suggesting a genetic cause of the manifestations. Other studies showed increases in the incidence of narcolepsy with H1N1 infection but not with the H1N1 vaccine, and case control studies in Europe showed no increased risk of narcolepsy with influenza vaccines.

Initial studies in the United States, which did not use the Pandemrix vaccine, showed no association with H1N1 influenza vaccine and narcolepsy, whereas later multicenter studies found increased incidences of narcolepsy associated with both H1N1 vaccines and H1N1 circulating virus. This back and forth of associations highlights the complexity of associating a rare neurologic disease with vaccinations with the risk of false attributions to the vaccine resulting in damaging consequences. The SARS-CoV-2 vaccines pose a similar challenge. The rapid vaccination of a very large population means that it is difficult to distinguish between manifestations that are causally related and those that are coincidental.

Fraudulent Claims of Vaccine-Associated Complications Have Further Eroded Public Confidence in the Vaccines

The measles, mumps, and rubella vaccine was reported to cause autism based on a case series and the claim that measles virus could be detected in blood cells from patients with autism. This claim has been refuted, and several subsequent studies failed to find an association. Ultimately, the Institute of Medicine (now called the National Academy of Medicine), after reviewing all the evidence, concluded that there was no association of autism with the vaccine, and the original article was retracted.

Neurologists continue to expand our knowledge base of the nervous system complications of infectious diseases. It is therefore logical and critical that neurologists play a major role in leading research efforts into understanding the neurologic complications of vaccines. They are best trained and equipped to recognize neurologic manifestations of both infections and the side effects of the vaccines and may recognize phenotypes that give clues to underlying molecular mechanisms. Because the symptoms of these 2 different processes can overlap, it is important to differentiate between them and to treat them appropriately.
Vulnerable Populations and Underlying Mechanisms

Because vaccine-related neurologic complications occur in a small subpopulation of patients, determining the factors that make people vulnerable to developing these side effects may help prevent these complications. For example, immunocompromised individuals should not receive live attenuated vaccines because they may be vulnerable to complications of these vaccinations, and they may not mount an adequate immune response to other vaccines. For patients who are on immunosuppressive drugs for the treatment of autoimmune conditions, the timing of vaccination in relationship to the administration of the immunosuppressive therapy can be critical. For example, guidelines have been established for patients with multiple sclerosis taking these factors into consideration.\textsuperscript{23}

There is a great need to conduct research for identifying the underlying factors and subcellular mechanisms that result in the neurologic manifestations from vaccines. Questions that could be addressed include identification of comorbidities or genetic factors that increase susceptibility to these side effects; epidemiologic studies to determine what manifestations are common to most vaccines, which are unique and which may occur just by chance alone; develop in vitro models, animal models, and clinical studies to understand the immunopathogenesis of these illnesses and to determine the impact of the vaccines on individuals with underlying systemic or neurologic illnesses; and finally, conduct clinical trials that target these pathways to either pretreat individuals with underlying systemic or neurologic illnesses; and determine the impact of the vaccines on individuals with underlying systemic or neurologic illnesses; and finally, conduct clinical trials that target these pathways to either pretreat individuals to prevent the side effects or treat after the manifestations. Research may also guide the development of safer vaccines.

Prevention and Treatment

Most likely, mechanisms causing vaccine-mediated neurologic manifestations are related to aberrant immune responses. Hence, one would reason that immunotherapies would be a reasonable treatment option. In fact, several case reports and case series seem to support this approach.\textsuperscript{12,24} However, the type of treatment, dosages, and duration of treatments need to be further optimized. Clinical trials targeted at such manifestations are needed. Furthermore, it needs to be determined whether patients who may have developed adverse effects from one vaccine are at risk of similar effects with booster dosages of the same vaccine or with other vaccines and whether these can be prevented by prophylactically using small doses of corticosteroids or other immunomodulatory agents without compromising the desired antiviral immune responses from the vaccine.

Role of Various Organizations and Possible Solutions

Vaccine adverse event monitoring is not the portfolio of the NIH, which is focused on disease-oriented and fundamental research. The US Food and Drug Administration (FDA) evaluates the risks of the vaccines before approval. This is a rigorous process and picks up the common side effects. For example, the phase III randomized clinical trials of the mRNA vaccines show 12.5 additional serious adverse events per 10,000 vaccinated compared with placebo.\textsuperscript{25} Identification of rare side effects require exposure to large populations and postmarketing surveillance. Once the vaccines are approved, active surveillance continues through the US FDA’s biologic effectiveness and safety (BEST) system\textsuperscript{26} and through the Center for Disease Control and Prevention (CDC)’s vaccine safety datalink program.\textsuperscript{27} The scope of these programs needs to be expanded to be able to capture the rare neurologic complications. No one has primary responsibility for investigating the mechanisms of side effects of vaccines. In contrast, for therapeutic agents, the manufacturer is held responsible. The US FDA regulates them and may require active surveillance programs. The US FDA has an adverse reporting program called Medwatch. It is mandatory for pharmaceutical companies to report any side effects brought to their attention through this mechanism. Health professionals and consumers may also report side effects through this system. The US FDA keeps a close watch on these reports and can act accordingly by creating black box warnings, halting sales, modifying package insets, etc. Side effects of vaccines are co-monitored by the CDC and US FDA, through a system called the VAERS, which is similar to Medwatch. While vaccine manufacturers are required to report all adverse events that come to their attention, anyone can report a potential adverse event. Although well intentioned to capture information as broadly as possible, the major drawback is that there is no way to check the authenticity of the information and there is a high degree of variability of the details provided. They are often incomplete, inaccurate, and coincidental, and there might be multiple entries on the same individual.

There are global efforts to monitor the safety of vaccines. For example, the Coalition for Epidemic Preparedness Innovations has partnered with the Brighton Collaboration, through the World Health Organization’s (WHO) Task Force for Global Health to harmonize the safety assessment of vaccines through its Safety Platform for Emergency Vaccines Project.\textsuperscript{28} They have developed a number of tools and guidelines for monitoring safety and adverse events during vaccine clinical trials. It has also created a list of potential adverse events related to the SARS-CoV-2 vaccines.\textsuperscript{29} EnduraVigilance is a European system that manages and analyzes adverse events of medications that includes vaccines\textsuperscript{30}, and VigiBase is a WHO global database of potential side effects of medicinal products including vaccines.\textsuperscript{31} Analysis of the clinical trials and these databases confirm the risk of coagulation disorders and myocarditis with the mRNA vaccines (reviewed in reference 25). These analyses do not show a signal for neurologic adverse events that may be rare, or some manifestations are not considered as serious adverse events and thus maybe underreported. Furthermore, neurologic manifestations are often hard to diagnose, they require special expertise, and may...
require sophisticated investigations that are not readily available. The medical system is also overburdened, and patients report long wait times before they can see a neurologist. Considering the exposure of hundreds of millions or possibly billions of people to these vaccines, even a rare event could affect a substantial number of individuals. Thus, larger active surveillance programs that pay special attention to gathering information on neurologic complications and where information on neurologic complications and where information are gathered is necessary (Table 2).

In 2005, Congress passed the Public Readiness and Emergency Preparedness (PREP) Act. The act specifically affords to drug companies, immunity from actions related to the “manufacture, testing, development, distribution, administration and use of medical countermeasures against chemical, biological, radiologic and nuclear agents of terrorism, epidemics, and pandemics.” Thus, the bill provides immunity to drug companies from being sued for any unforeseeable side effect of vaccines, but they can be held responsible if there was any willful misconduct (42 US code 247-6d). The PREP Act created a fund called the Countermeasures Injury Compensation Program. This provides compensation to the people who may have been injured from the vaccine. This was performed to incentivize companies to take on the risk for the development of vaccines. However, no funds were obligated to provide any provisions for studying the underlying mechanisms of these side effects for developing ways to prevent them or for treating them. As a result, there is a gap in knowledge about the postmarketing neurologic side effects of vaccines, and lack of an organized effort to provide a definitive diagnosis or develop treatments for these patients. A simple solution might be to convene all stakeholders preferably at a global level to investigate the side effects and provide funding to conduct research to study and treat them (Table 2). Cooperation of vaccine manufacturers would be critical because only they have access to proprietary information about the vaccines. This will help develop a better understanding of the spectrum of postmarketing side effects, identify those that are causally related, and help develop ways of mitigating them. Above all, it will build public trust and will go a long way toward reassuring them about the safety of vaccines. Unless these steps are taken, an unvaccinated population will remain the biggest threat to all public health measures with grave consequences.

Acknowledgment
The author thanks Drs. Walter Koroshetz, Nina Schor, Tara Schwetz, and Tory Johnson at the NIH and Drs. Janet Woodcock and Peter Marks at the US FDA for carefully reading the paper and for helpful comments.

Study Funding
NS3130 from National Institute of Neurological Disorders and Stroke, NIH.

Disclosure
The author reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Table 2 Future Research Needed to Study Neurologic Complications of Vaccines

| 1. Expansion of active surveillance programs | | |
| 2. Develop tools for gathering precise information on neurologic complications | | |
| 3. Genetic susceptibility studies | | |
| 4. Immune profiling of individuals with neurologic manifestations | | |
| 5. Determine association with comorbidities | | |
| 6. Develop animal models | | |
| 7. Conduct clinical trials for the prevention and treatment of adverse events | | |

references
3. Poliomyelitis. World Health Organization. who.int/health-topics/polio/myelitis#tab=tab_1.
6. Dubensky TW Jr, Skoble J, Lauer P, Brockstedt DG. Killed but metabolically active vaccines. This will help develop a better understanding of the mechanism of these side effects.

Appendix Author

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<tr>
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<tr>
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<td>Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data</td>
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CRediT authorship contribution statement

Avindra Nath, MD: Conceptualization, Data curation, Writing - review & editing.

Table 2

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Received by Neurology September 28, 2022. Accepted in final form March 9, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor Rebecca Burch, MD.

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Neurology 2023;101;621-626 Published Online before print April 25, 2023
DOI 10.1212/WNL.0000000000207337

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