Doctor—Should I get the COVID-19 vaccine? Infection and immunization in individuals with neuromuscular disorders

Sasha A. Živković MD, PhD | Gregory Gruener MD, MBA, MHPE | Pushpa Narayanaswami MD | the AANEM Quality and Patient Safety Committee

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic has raised several concerns about the care of individuals with neuromuscular disorders (NMDs). With the recent Emergency Use Approval (EUA) of two COVID-19 vaccines (PfizerBioNTech and Moderna) by the US Food and Drug Administration (FDA) and more in the pipeline, questions arise regarding the safety and efficacy of these vaccines overall, and also in several special populations including individuals with NMDs. The course of NMDs varies depending on the underlying etiology and pathophysiology and can be affected by concomitant illnesses and infections. Weakness of respiratory or bulbar muscles result in aspiration risk due to dysphagia, impaired ability to take a deep breath, impaired cough reflex, and ineffective airway clearance of secretions with resultant atelectasis and pneumonia. Special concerns in some of these disorders include the use of immunosuppressive and immunomodulating (IS/IM) agents, which may increase susceptibility to infections and concurrently reduce the humoral response to immunizations. This Practice Topic article addresses the following topics with an emphasis on COVID-19: (a) infection-related disease
exacerbations in patients with NMDs; (b) infections associated with de novo NMDs; (c) risk of infections related to IS/IM treatments of NMDs; (d) immunization of patients with NMDs; and (e) association of immunization with de novo development of NMDs.

Immunization against a disease may be achieved by natural infection or by vaccination against a specific agent or agents. The aim of vaccination is to generate an immune response against a particular antigen and protect susceptible populations from communicable diseases. This may be accomplished by the administration of a living modified agent (“live vaccine”: eg, yellow fever vaccine), a suspension of killed organisms (eg, pertussis vaccine), a protein expressed in a heterologous organism (eg, hepatitis B vaccine), or an inactivated toxin (eg, tetanus). In this Practice Topic, we use the terms immunization and vaccination interchangeably to refer to immunity developed in response to vaccines.

2 | INFECTIONS AND UNDERLYING NMDS

An increased risk mortality from influenza and increased rates of pneumococcal disease have been associated with NMDs. In a large population-based cohort study, MG was associated with a 39% increased risk of serious infections, mainly respiratory, compared with 19.4% in the general population, over a mean follow-up period of 5.4 years (multivariate analysis with an adjusted hazard ratio, 1.39; 95% confidence interval [CI], 1.28-1.51). Acute infections may, in turn, worsen respiratory function further, resulting in acute respiratory failure and the need for ventilatory assistance. Exacerbations of myasthenia gravis (MG) are commonly associated with infections. In a recent study of 250 cases of myasthenic crisis requiring mechanical ventilation, the trigger for crisis was an infection in almost half of the patients. In a retrospective cohort of patients under 21 years age and hospitalized with community-acquired influenza, concomitant NMDs were associated with higher risk of respiratory failure.

3 | INFECTIONS ASSOCIATED WITH DE NOVO NMDS

Infectious agents may directly cause NMDs (eg, cytomegalovirus [CMV] polyradiculopathy) or may trigger a postinfectious immune reaction (eg, acute inflammatory demyelinating polyneuropathy [AIDP] or Guillain-Barré syndrome [GBS]). Acute anterior horn-cell involvement or poliomyelitis/acute flaccid paralysis is a feature of several viral infections, including poliovirus, West Nile virus, and enterovirus D68. Human immunodeficiency virus (HIV) infection is associated with several types of NMDs, either directly or due to opportunistic infections. Distal symmetrical, axonal, predominantly sensory polyneuropathy is the most common type of neuropathy in individuals with HIV. Mononeuritis multiplex due to vasculitis is a rare complication of HIV infection. A progressive polyradiculopathy due to opportunistic infection with CMV is well-known, but is also associated with lymphoma, tuberculosis, syphilis, and cryptococcus. An amyotrophic lateral sclerosis (ALS)-like syndrome has been described with HIV infection. HIV-associated polymyositis, nemaline myopathy, dermatomyositis, inclusion-body myositis, and necrotizing myopathy have been reported. Reactivation of varicella zoster virus (VZV) causes herpes zoster or shingles, which is characterized by dermatomal vesicular eruption and pain affecting cranial or spinal nerves, and may be followed by postherpetic neuralgia. Reactivation of VZV infection is also associated with myelitis, cranial neuropathies, and rarely with segmental motor paresis resulting from VZV-related radiculopathies, plexopathies, or mononeuropathies. Leprosy, caused by Mycobacterium leprae, is a common cause of neuropathy in developing countries. Several bacteria, viruses, fungi, and parasites can cause infectious myositis.

Postinfectious de novo NMD is best exemplified by the association of AIDP/GBS with antecedent infections (Campylobacter jejuni, influenza, CMV, Epstein-Barr virus, Mycoplasma pneumoniae, Hemophilus influenzae, hepatitis E, Zika virus), where molecular mimicry is the proposed pathogenic mechanism. One study showed that 18% of GBS patients during an influenza outbreak had serologic evidence of influenza. There are recent reports of COVID-19–associated GBS (Section F). Infections can also trigger multisystemic and peripheral nerve vasculitides, including cryoglobulinemia (hepatitis C) and polyarteritis nodosa (hepatitis B [HBV]). Most of these infections are not vaccine-preventable except for influenza, H influenzae, and H zoster, and, most recently, COVID-19.

4 | IMMUNOSUPPRESSION AND RISK OF INFECTIONS IN INDIVIDUALS WITH NMDS

IS/IM agents are commonly used in the treatment of autoimmune neuromuscular disorders, and vaccinations have a major role in reducing the morbidity associated with vaccine-preventable infections in this population. There is a common perception that IS agents increase the risk of infections, both typical and atypical. A retrospective review of 631 patients with MG, chronic inflammatory demyelinating polyneuropathy (CIDP), and dermatomyositis who were on IS/IM agents revealed an infection rate of 19% in all three diseases, with pneumonia being the most frequent. There was a significant independent association between infections and the use of plasmapheresis, mycophenolate mofetil, and corticosteroids in multivariate analyses. Line infections due to plasmapheresis were not separately analyzed in that retrospective study. Corticosteroids are associated with an increased risk of infections, including reactivation of latent tuberculosis. B-cell-depleting therapies, such as rituximab, can reactivate HBV infections. The risk of reactivation is estimated at over 10% with rituximab or high-dose corticosteroid therapy (>20 mg/day prednisone for >14 consecutive days). The risk of HBV reactivation with azathioprine, methotrexate, or low-dose corticosteroids (<10 mg/day prednisone) is estimated at less than 1%. Reactivation of VZV infections has also been reported with the use of rituximab. Progressive multifocal leukoencephalopathy (PML) due to reactivation of John Cunningham virus (JC virus) infection is the most serious
rituximab. This drug appears to have the most profound effect on cells. Antibody responses may be impaired for at least 6 months after pneumococcal vaccines. The efficacy of other vaccines is also likely to affect the immune response to vaccines, including influenza vaccine and tetanus toxoid. The vaccination campaign for swine influenza (H1N1) in 1976 was associated with an increased risk of GBS of 1 per 100 000 vaccinated individuals. Subsequent studies have reported varying risks of GBS (none, lower, or higher) associated with various influenza vaccines. At this time, the risk of GBS after influenza infection and the complications of influenza infection appear to outweigh the risk of influenza vaccine associated GBS. In CIDP, antecedent infections and vaccinations have been reported in 12% and 1.5%, respectively, within 6 weeks from onset. Worsening of CIDP symptoms after tetanus vaccination has been reported in 8.7% of patients, but only 1 of 65 patients required treatment within 2 months from immunization. There is no evidence of an association of idiopathic inflammatory myopathies and vaccinations, and the H1N1 vaccination appears to be safe and effective in patients with inflammatory myopathies. Overall, however, the risk of vaccination-triggered NMDs appears to be low, and should be evaluated in the context of the risk of NMDs being triggered or worsened by vaccine preventable infections.

5 | EFFECTIVENESS OF VACCINATIONS IN IMMUNOSUPPRESSED INDIVIDUALS WITH NMDS

Altered immunocompetence may reduce the effects of vaccination. However, there is limited information on the effectiveness of vaccines in individuals who are on IS/IM agents. Methotrexate reduces the humoral response to pneumococcal vaccine. Rituximab depletes CD19+ B cells, pre-plasma cell blasts, and interferon-γ–secreting T cells. Antibody responses may be impaired for at least 6 months after rituximab. This drug appears to have the most profound effect on the immune response to vaccines, including influenza vaccine and pneumococcal vaccines. The efficacy of other vaccines is also likely to be affected. High-dose immunosuppression (prednisone >20 mg/day for >14 consecutive days, azathioprine >3 mg/kg per day, methotrexate >0.4 mg/kg per week) is more likely to affect response to vaccination than low doses.

6 | RISK OF VACCINATIONS FOR DEVELOPMENT OF DE NOVO NMDS

GBS has been described in case reports and case series after immunizations for influenza, polio, rabies, meningococcus, measles, mumps, and infectious complication of IS therapy, for which there is no effective vaccine or treatment currently available. Three cases of PML were reported in MG, one rituximab related, with prior use of other IS agents, and the others related to azathioprine, corticosteroids, and intravenous immunoglobulin (IVlg). IS agents increase the risk of Pneumocystis jirovecii (previously P carinii) pneumonia (PJP). The risk of PJP is higher in patients receiving corticosteroids in combination with other IS agents. In a Cochrane Review of prophylactic trimethoprim/sulfamethoxazole (TMP/SMZ) in patients with leukemia, solid-organ transplantation, or autologous bone marrow transplant, there was an 85% reduction in the occurrence of PJP in patients receiving prophylaxis compared with no treatment or treatment with fluoroquinolones, which are inactive against PJP (relative risk, 0.15; 95% confidence interval, 0.04-0.62; 10 trials, with 1000 patients). Adverse events were not significantly different with TMP/SMZ and no severe adverse events were noted. Leukopenia was reported as more frequent in the TMP/SMZ group in one study, but the difference was not significant. Eculizumab is associated with a risk of serious meningococcal infections (meningitis, sepsis). It binds to complement protein C5 to block cleavage into C5a and C5b, thus preventing the combination of C5b with complement proteins C6 to C9, which form the membrane attack complex (MAC). The lack of MAC inhibits the ability of the immune system to respond effectively to acquired Neisseria infections, due to the lack of adequate serum bactericidal activity and impaired opsonization with reduced phagocytic destruction of the encapsulated organism.

7 | COVID-19 INFECTION, VACCINATION, AND NEUROMUSCULAR DISORDERS

As of December 29, 2020, the COVID-19 pandemic has affected more than 79 million individuals worldwide with over 1.7 million deaths. COVID-19 is caused by the severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2), a member of the virus family Coronaviridae, which contains four genera. Coronaviruses are single-stranded, enveloped RNA viruses, named for their crownlike appearance on electron microscopy. The SARS-CoV-2 sequence is similar to other human coronaviruses that are responsible for 15% of all cases of acute viral nasopharyngitis of the “common cold” and belongs to the betacoronavirus genus. SARS-CoV-2 has four structural proteins: the spike protein covers the surface of SARS-CoV-2 and binds to the host-cell angiotensin-converting enzyme-2 receptor, mediating viral cell entry. It is targeted by host-neutralizing antibodies. Envelope proteins form viroporins, small hydrophobic proteins necessary for viral assembly/release and mediate pathogenicity and cytotoxicity. The membrane protein is the most abundant structural protein, providing a scaffold in assembly of the virus. The nucleocapsid protein binds to viral RNA to form a ribonucleoprotein, which facilitates host-cell entry and interaction with cellular processes. Recently, new variants of SARS-CoV-2 have been described in various parts of the world, including the UK, South Africa, and Nigeria. The variant identified in the UK is referred to as SARS-CoV-2 VOC 202012/01 (the first variant of concern from December 2020). This variant appears to have increased transmissibility.

The clinical picture of COVID-19 ranges from an asymptomatic illness to mildly symptomatic with respiratory or gastrointestinal symptoms, to a severe illness with coagulopathy and systemic multiorgan failure. Symptoms attributed to peripheral nervous system (PNS) involvement were reported in 19 of 214 (8.9%) hospitalized patients with COVID-19 in Wuhan, China. Impaired smell and taste were the
most frequent symptoms attributed to PNS involvement. Nerve pain and skeletal muscle injury were reported in 2.3% and 10.7%, respectively, but skeletal muscle injury was not further characterized, as most diagnoses rested on subjective symptoms without complete examinations. Most patients with skeletal muscle injury had elevated creatine kinase (CK) levels (median, 400 U/L; range, 203-12 216 U/L).68

COVID-19 has been associated with parainfectious (during the acute infection) or postinfectious GBS and all common variants of GBS have been reported.26,67 The exact prevalence of COVID-19-associated GBS remains uncertain because of potential ascertainment bias and selective reporting but appears to be low.26,27 It has been suggested that the spike protein of SARS-CoV-2 binds to sialic acid residues of gangliosides. This cross-reactivity to peripheral nerve gangliosides may trigger an immune reaction by molecular mimicry, resulting in GBS.26,69-71 However, anti-ganglioside antibodies have been only infrequently detected in reported cases of COVID-19-associated GBS.26 Other neuromuscular complications reported in COVID-19 patients include myalgias and elevated CK levels, myositis, critical illness myopathy, mononeuropathies, and entrapment neuropathies due to prolonged prone positioning.72-79 It remains uncertain whether these neuromuscular complications of COVID-19 are due to direct viral invasion, an inflammatory cytokine response to the virus, or to other factors. One patient with COVID-19 and generalized muscle weakness (proximal > distal) and CK 29 800 IU/L was noted to have mild perivascular inflammation on muscle biopsy, abnormal sarcolemmal and sarcoplasmic expression of major histocompatibility complex class I (MHC-1) antigen, and abnormal myxovirus resistance protein (MxA) expression on the sarcolemma and sarcoplasm. MxA protein is expressed in response to viral infections and is induced by type I interferon. The authors indicated that the expression of this protein suggests a toxic effect of increased interferon-I expression (type I interferonopathy).80

The worldwide devastation wrought by the COVID-19 pandemic has stimulated a large number of clinical trials investigating different vaccines for COVID-19. The antigenic targets include inactivated whole virus, subunit formulations that utilize one or more viral components, nanoparticle protein formulations using particulate antigens, and nucleic acid vaccines that utilize genetic material (DNA or RNA) to stimulate an immune response.81 Messenger RNA (mRNA)-based vaccines expressing the target antigen are delivered into the cell cytoplasm without incorporation to the human genome, as in the case of DNA-based vaccines.81-83 Vector vaccines use a modified virus (the vector) to deliver the genetic code for an antigen, such as the COVID-19 spike protein, into human cells. The infected cells then produce the antigen mimicking natural infection and prompting an immune response.81

As of December 10, 2020, studies of phase 1, 2, and 3 trials using nine different vaccines have been published. The Infectious Disease Society of America (IDSA) website provides updates on available studies.84 The first vaccine to receive EUA by the FDA for individuals 16 years and older was the Pfizer-BioNtech COVID-19 vaccine (BNT162b2) on December 11, 2020. BNT162b2 is a lipid nanoparticle formulated nucleoside-modified mRNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. In a multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, 43 448 persons 16 years of age or older were randomly assigned to BNT162b2 in a 1:1 ratio to two doses, 21 days apart, of either placebo or vaccine (30 μg per dose). It was found to confer 95% protection against COVID-19. Mild-to-moderate injection-site pain was the most frequent local reaction, reported in 71% to 83% of older (>55 years) and younger (16-55 years) participants, respectively, after the first dose, compared with 9% and 14% of those receiving placebo. Fatigue and headache were the most frequent systemic side effects. Severe systemic effects were reported in more than 2% of participants. A median of at least 2 months of safety data was available for 37 706 participants, and the safety profile was reported as similar to that of other viral vaccines. Four related serious adverse events were reported: shoulder injury related to vaccine administration; right axillary lymphadenopathy; paroxysmal ventricular arrhythmia; and right leg paresthesia.85 Post-EUA, during clinical use, a few cases of anaphylaxis to the vaccine have been reported. The US Centers for Disease Control and Prevention (CDC) states, “If you have ever had a severe allergic reaction to any ingredient in a COVID-19 vaccine, CDC recommends that you should not get that specific vaccine.”86

The Moderna mRNA vaccine mRNA-1273 received EUA by the FDA on December 18, 2020 for individuals 18 years and older. A phase 3, observer-blinded randomized, controlled trial of 30 420 individuals randomly assigned at a 1:1 ratio to receive either vaccine or placebo reported symptomatic COVID-19 illness in 185 participants in the placebo group and 11 participants in the vaccine group. Vaccine efficacy was 94.1% (95% CI, 89.3%-96.8%; P < .001), with a median follow-up of 64 days after dose 2. Thirty participants had severe COVID-19, with all receiving placebo. Safety data with a median 7-week follow-up did not reveal specific safety concerns. The most common adverse reactions associated with mRNA-1273 were injection-site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of the participants. There were three reports of Bell palsy in the vaccine group and one in the placebo group.87 The effectiveness of both COVID-19 mRNA vaccines against the new variants of SARS-CoV2 continues to be investigated.85,66

As the COVID-19 vaccination program rolls out in the United States and other countries, the allocation of vaccines has been an issue with demand outpacing initial supply. The Advisory Committee on Immunization Practices (ACIP) recommendations for phased COVID-19 vaccine allocation have been adopted by the CDC, and recommended as a guideline for state health departments. The overall principles informing allocation are to: (a) decrease death and serious disease as much as possible; (b) preserve functioning of society; (c) reduce the extra burden the disease is having on people already facing disparities; and (d) increase the chance for everyone to enjoy health and well-being. The ACIP guided their decisionmaking based on four ethical principles: (a) maximize benefits and minimize harms; (b) mitigate health inequities; (c) promote justice; and (d) promote transparency. With these guiding principles, three initial phases of vaccine allocation have been recommended: phase 1a—for long-term-care
facility residents and health-care personnel; phase 1b—for persons ≥75 years age and frontline essential workers; phase 1c—for persons aged 65 to 74 years, persons aged 16 to 64 years with high-risk medical conditions, and essential workers not included in phase 1b.88,89

8 | VACCINATION AND INFECTION PROPHYLAXIS IN INDIVIDUALS WITH NMDS

NMDSs are diverse, affecting all age groups. From the perspective of infections and immunizations, two fairly distinct groups of NMDSs emerge: those that are autoimmune and frequently treated with IS/IM agents, and those that are inherited/degenerative and treated mainly with supportive management. It is possible that the risk of infections in individuals with NMDS receiving long-term IS/IM treatments may be greater than that in individuals with NMD who are not receiving these treatments, although data to support this are sparse. In addition, distinct questions regarding immunization arise in these two groups. Underlying cardiac and respiratory dysfunction places individuals with NMDSs at greater risk of serious complications and increased mortality from infections such as influenza, regardless of treatment with IS/IM agents.90 Additional considerations in individuals treated with NMD on IS/IM agents include vaccine-related worsening of the underlying disorder, triggering of new autoimmune NMDSs, and suboptimal vaccine efficacy. The following are general recommendations for immunization in patients with NMDSs. All of these are subject to change and should be reviewed periodically. Table 1 provides a list of the common inactivated and live attenuated vaccines, and Table 2 describes specific vaccine recommendations in immunocompetent and immunocompromised hosts according to the CDC.

a. | General recommendations

1. The rationale for vaccination, specific issues relevant to the individual, the benefits and risks of immunization, and the limitations of available data should be discussed. Informed, shared decisionmaking is an important part of this process.

2. Age-appropriate immunization schedules recommended by authorities such as the CDC or World Health Organization (WHO) should be followed in individuals with NMDSs, with some modifications in those with reduced immunocompetence.30,40,44

3. In individuals with reduced immunocompetence, live vaccines may cause severe systemic infections and are contraindicated.41 Individuals with reduced immunocompetence should be counseled that they should avoid the nasal spray (live) influenza vaccine and should receive the injectable inactivated vaccine.41

4. Because full immunity after vaccination may not be achieved in patients who are immunosuppressed, inactivated vaccines should be updated, if possible, 2 weeks before starting IS agents (4 weeks before starting IS agents for live vaccines). Patients vaccinated within a 14-day period before starting IS agents should be revaccinated at least 3 months after the treatment is discontinued.93 Because of the attenuating effect of rituximab on multiple vaccines, it is recommended that all scheduled immunizations be completed 4 weeks before commencing rituximab and other B-cell–depleting therapies, or at least 6 months after the treatment is completed.91,92

5. In patients receiving IVlg, response to varicella and measles/mumps/rubella and other vaccines may be attenuated because of the presence of passive antibodies interfering with replication of attenuated virus and subsequent immune response. It is recommended that the vaccines be given 14 days before the next dose of IVlg, and then repeated 8 months after the treatment is completed.41

6. In immunosuppressed individuals, measuring serologic titers of antibodies postvaccination may inform the need to revaccinate, but this is not a uniform practice. Ongoing treatment with IVlg may interfere with the accuracy of serologic testing.

7. If IS therapy is planned, screening for latent infections such as hepatitis B, hepatitis C, HIV, and tuberculosis should be performed as per the manufacturer’s prescribing information. It is suggested that screening for both hepatitis B and hepatitis C be performed before initiating rituximab in patients with rheumatoid arthritis.93 Patients receiving corticosteroids (≥15 mg/day prednisone equivalent) or other IS agents in the setting of organ transplantation are considered to be at high risk of reactivation of latent tuberculosis.94 Although data specific to individuals with NMDSs taking IS agents are not available, screening for these disorders may be appropriate in these individuals as well.

8. Infectious disease consultation should be sought to manage latent infections detected by screening before starting IS agents and to monitor for reactivation during IS treatment.

b. | Recommendations for specific vaccines or drugs

1. The ACIP recommends that persons who have developed GBS within 6 weeks of receipt of an influenza vaccine generally should
not receive influenza vaccine again unless they are at high risk from influenza complications.95 Patients should be counseled that the risk of influenza probably outweighs the risk of recurrent GBS if they are at risk of serious complications from influenza.

2. Two types of pneumococcal vaccines are available in the United States: the pneumococcal 13-valent vaccine (PCV13) and the pneumococcal 23-valent polysaccharide vaccine (PPSV23). Patients with NMDs and respiratory or cardiac involvement should receive one dose of PPSV23. If immunosuppressed, patients should receive one dose of PCV13, followed by one dose of PPSV23 8 weeks later, and then a second dose of PPSV23 5 years after the first dose (Table 2).96

3. The inactivated zoster vaccine (Shingrix) is recommended (two doses given 2-6 months apart) in anticipation of IS therapy or for individuals on low-dose IS therapy. At this time, it is not recommended for immunocompromised persons or those receiving high-dose IS therapy.97 The live inactivated zoster vaccine (Zostavax) is no longer available in the United States.

4. Individuals should receive the first doses of quadrivalent (meningococcal ACWY) and group B meningococcal vaccination at least 2 weeks before starting therapy with complement inhibitors such as eculizumab. As meningococcal vaccination may not fully prevent meningococcemia in patients treated with complement inhibitors, the CDC recommends consideration of antibiotic prophylaxis.98 In addition, meningococcal vaccine boosters (both quadrivalent and serogroup B) are recommended for patients with continued risk of meningococcal infections (including ongoing treatment with complement inhibitors).99

5. There are no published guidelines for PJP prophylaxis in individuals with NMDs or receiving IS agents. However, prophylaxis may be offered to patients receiving >20 mg of prednisone equivalent for over 1 month who are also on a second IS agent.100

### TABLE 2: Recommended adult immunization schedule for individuals 19 years of age and older, USA105

| Vaccine                              | Not immunosuppressed                                                                 | Immunosuppressed                                                                 |
|---------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Influenza (IIV—inactivated, LAIV—live) | 1 dose annually (IIV or LAIV).                                                       | 1 dose annually (IIV only).                                                       |
| Tetanus, diphtheria, pertussis (Tdap or td) | 1 dose Tetanus, diphtheria, pertussis (Tdap), then Tetanus, diphtheria or Pertussis, diphtheria, pertussis (Td/Tdap) booster every 10 years. | Same.                                                                            |
| Measles, mumps and rubella (MMR)      | If no immunityb: 1 dose.                                                            | Contraindicated.d                                                                |
| Varicella (VAR)                       | If no immunity to varicellaa: 1 dose.                                               | Contraindicated.d                                                                |
| Zoster recombinant (RZV)             | Age ≥50 years: 2-dose series 2-6 months apart.                                       | Zoster vaccination not recommended.                                              |
| Human papillomavirus vaccination (HPV) | 2- or 3-dose series for adults through age 26 years.                                 | Same.                                                                            |
| Pneumococcal vaccination (PCV13, PPSV23) | (a) Age ≥65 years: 1 dose PPSV23 and shared clinical decision making for 1 dose PCV 13. (b) If PPSV23 before age 65 years, administer 1 dose PPSV23 at least 5 years after previous dose. | 1 dose PCV13 followed by 1 dose of PPSV23 at least 8 weeks later, then another dose of PPSV23 at least 5 years after previous PPSV23; at age ≥65 years, administer 1 dose of PPSV23 at least 5 years after most recent PPSV23. |
| Hepatitis A (Hep. A)                 | Individuals at risk: 2- or 3-dose series.                                           | Same.                                                                            |
| Hepatitis B (Hep. B)                 | Individuals at risk: 2- or 3-dose series.                                           | Same.                                                                            |
| Meningococcal vaccine (4-valent men ACWY; men B) | First-year college students who live in residential housing and military recruits: 1 dose men ACWY. Adolescents and young adults age 16-23 years not at increased risk: consider 2-dose series of men B. | Complement inhibitors (eculizumab): (a) Men ACWY: 2-dose series men ACWY at least 8 weeks apart and booster every 5 years if risk remains. (b) Men B: 2- or 3-dose primary series; 1 dose men B booster 1 year after primary series and revaccinate every 2-3 years if risk remains. |
| Hemophilus influenza type B (HiB)     | Individuals at risk.                                                                | Same.                                                                            |

---

**COVID-19 vaccination in individuals with NMDs**

Although NMD patients have not been listed as a high risk for COVID-19, and are currently not considered in the planned allocation of early-phase COVID-19 vaccinations, ACIP and CDC recommendations are expected to expand as large enough quantities of vaccine become available.80,89
1. COVID-19 vaccination is recommended for persons 16 to 18 years of age and older, with the ACIP/CDC recommended allocation schedule based on perceived risk. 

2. The same brand of COVID-19 vaccine should be used for both initial and booster injections. They should not be administered within 14 days of other vaccines. 

3. All individuals with NMDs who are not taking IS agents should be encouraged to receive COVID-19 vaccines because the risk of COVID-19 infections likely outweighs the potential risks of the vaccine. 

4. Individuals with NMDs who are taking IS/IM agents should be counseled that there are no data currently regarding the safety or efficacy of COVID-19 mRNA vaccines in this population, but the vaccine benefits of reducing COVID-19 infection likely outweigh the potential risks. Even reduced efficacy may confer benefits against COVID-19 infections. 

5. Individuals with autoimmune NMDs should be counseled that no data are currently available on the safety and efficacy of mRNA COVID-19 vaccines in this population. An increased risk of developing autoimmune or inflammatory disorders was not observed in clinical trial participants who received an mRNA COVID-19 vaccine compared with placebo. There are no data regarding the risk of exacerbation of autoimmunity NMDs by the COVID-19 vaccine. Persons with autoimmune conditions who have no contraindications to vaccination may receive an mRNA COVID-19 vaccine. 

6. Persons with a history of GBS and autoimmune conditions may receive COVID-19 mRNA vaccines unless they have other contraindications to vaccination. 

7. Individuals should be counseled that the vaccine does not carry the risk of inducing systemic COVID-19 infection, and that it does not alter their DNA. 

8. Known adverse effects of the vaccine should be discussed and patients should be encouraged to participate in vaccine safety tracking programs such as V-safe by the CDC. 

9. Based on current knowledge, it is believed that both COVID-19 mRNA vaccines in present use are unlikely to pose a risk to the pregnant person or fetus, but the potential risks are unknown. If pregnant women are a part of a group that is recommended to receive a COVID-19 vaccine, they should discuss the vaccination with their health-care team to help them make an informed decision. 

ACKNOWLEDGMENTS

The authors thank Carrie Winter and Millie Suk (AANEM staff), Shirllyn Adkins JD (Executive Director of the AANEM), and the Board of Directors of the AANEM for their help and input. 

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. 

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. 

REFERENCES

1. US Food and Drug Administration. EUA for first Covid19 vaccine. December 11, 2020. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vac. Accessed December 30, 2020. 

2. US Food and Drug Administration. Moderna COVID-19 vaccine EUA letter of approval. December 18, 2020. https://www.fda.gov/media/144636/download. Accessed December 30, 2020. 

3. Panitch HB. Respiratory implications of pediatric neuromuscular disease. Respir Care. 2017;62:826-848. 

4. Kimbrell DA, Beutler B. The evolution and genetics of innate immunity. Nat Rev Genet. 2001;2:256-267. 

5. Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ. 2013;347:f5061. 

6. Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis. 2014;1:ofu024. 

7. Kassardjian CD, Widdifield J, Paterson JM, et al. Serious infections in patients with myasthenia gravis: population-based cohort study. Eur J Neurol. 2020;27:702-708. 

8. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. J Neurol. 2018;265:1251-1258. 

9. Neumann B, Angstwurm K, Mergenthaler P, et al. Myasthenic crisis demanding mechanical ventilation: a multicenter analysis of 250 cases. Neurology. 2020;94:e299-e313. 

10. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. JAMA. 2005;294:2188-2194. 

11. Kidd D, Williams AJ, Howard RS. Poliomyelitis. Postgrad Med J. 1996;72:641-647. 

12. Leis AA, Stoking DS. Neuromuscular manifestations of west nile virus infection. Front Neurol. 2012;3:37. 

13. Helferich J, Knoester M, Van Leeuwer BC, et al. Acute flaccid myelitis and enterovirus D68: lessons from the past and present. Eur J Pediatr. 2019;178:1305-1315. 

14. Robinson-Papp J, Simpson DM. Neuromuscular diseases associated with HIV-1 infection. Muscle Nerve. 2009;40:1043-1053. 

15. Pardo CA, McArthur JC, Griffin JW. HIV neuropathy: insights in the pathology of HIV peripheral nerve disease. J Peripher Nerv Syst. 2001;6:21-27. 

16. Manji H. Neuropathy in HIV infection. Curr Opin Neurol. 2000;13:589-592. 

17. Kaku M, Simpson DM. Neuromuscular complications of HIV infection. Handb Clin Neurol. 2018;152:201-212. 

18. Alfaahd T, Nath A. Retroviruses and amyotrophic lateral sclerosis. Antiviral Res. 2013;99:180-187. 

19. Elliott KJ. Other neurological complications of herpes zoster and their management. Ann Neurol. 1994;35(Suppl):S57-S61. 

20. Corral C, Quereda C, Muriel A, Martinez-Ulloa PL, Gonzalez-Gomez FJ, Corral I. Clinical spectrum and prognosis of neurological complications of reactivated varicella-zoster infection: the role of immunosuppression. J Neurol. 2020;26:696-703. 

21. Jones LR Jr, Reda H, Watson JC. Clinical, electrophysiologic, and imaging features of zoster-associated limb paresis. Muscle Nerve. 2014;50:177-185. 

22. Ooi WW, Sririvasan J. Leprosy and the peripheral nervous system: basic and clinical aspects. Muscle Nerve. 2004;30:393-409. 

23. Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. Clin Microbiol Rev. 2008;21:473-494. 

24. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388:717-727. 

25. Sivadon-Tardy V, Orlikowski D, Porcher R, et al. Guillain-Barré syndrome and influenza virus infection. Clin Infect Dis. 2009;48:48-56.
26. Caress JB, Castoro RJ, Simmons Z, et al. COVID-19-associated Guillain-Barré syndrome: the early pandemic experience. Muscle Nerve. 2020;62:485-491.
27. Fragiel M, Miro O, Llorens P, et al. Incidence, clinical characteristics, risk factors and outcomes of Guillain-Barre syndrome in patients with Covid-19. Ann Neurol. 2020.
28. Authier FJ, Bassez G, Payan C, et al. Detection of genomic viral RNA in nerve and muscle of patients with HCV neuropathy. Neurology. 2003;60:808-812.
29. de Boysson H, Guillevin L. Polyarteritis nodosa neurologic manifestations. Neurol Clin. 2019;37:345-357.
30. Cartwright SL, Cartwright MS. Health maintenance for adults with neuromuscular diseases on immunosuppression. Muscle Nerve. 2019;59:397-403.
31. Prior DE, Nurre E, Roller SL, et al. Infections and the relationship to treatment in neuromuscular autoimmunity. Muscle Nerve. 2018;57:927-931.
32. Malpica L, Moll S. Practical approach to monitoring and prevention of infectious complications associated with systemic corticosteroids, antimetabolites, cyclosporine, and cyclophosphamide in nonmalignant hematologic diseases. Hematology Am Soc Hematol Educ Program. 2020;2020:319-327.
33. Smalls DJ, Kiger RE, Norris LB, et al. Hepatitis B virus reactivation: risk factors and current management strategies. Pharmacotherapy. 2019;39:1190-1203.
34. Aksoy S, Harputluoglu H, Kilicak S, et al. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma. 2007;48:1307-1312.
35. Cortese I, Reich DS, Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat Rev Neurol. 2021;17:37-51.
36. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021;96:114-122.
37. Avino LJ, Naylor SM, Roescker AM. Pneumocystis jirovecii pneumonia in the non-HIV-infected population. Ann Pharmacother. 2016;50:673-679.
38. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev. 2014;CD005590, 2010;CD005590.
39. Konar M, Granoff DM, Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. Blood. 2017;130:891-899.
40. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:e44-e100.
41. Advisory Committee on Immunization Practices. Altered immunocompetence. general best practice guidelines for immunization: best practices guidance of the Advisory Committee on Immunization Practices (ACIP). https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html. Accessed December 30, 2020.
42. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor alpha, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2014;66:1016-1026.
43. Nazi I, Kelton JG, Larché M, et al. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. Blood. 2013;122:1946-1953.
44. Esposito S, Bruno C, Berardinielli A, et al. Vaccination recommendations for patients with neuromuscular disease. Vaccine. 2014;32:5893-5900.
45. Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. Drug Saf. 2009;32:309-323.
46. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. Am J Epidemiol. 1979;110:105-123.
47. Haber P, DeStefano F, Angulo FJ, et al. Guillain-Barré syndrome following influenza vaccination. JAMA. 2004;292:2478-2481.
48. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992–1993 and 1993–1994 influenza vaccines. N Engl J Med. 1998;339:1797-1802.
49. Grave C, Boucheron P, Rudant J, et al. Seasonal influenza vaccine and Guillain-Barré syndrome: a self-controlled case series study. Neurology. 2020;94:e2168-e2179.
50. Vellozzi C, Iqbal S, Broder K. Guillain-Barré syndrome, influenza, and influenza vaccination: the epidemiologic evidence. Clin Infect Dis. 2014;58:1149-1155.
51. Lehmann HC, Hartung HP, Kieseier BC, et al. Guillain-Barré syndrome after exposure to influenza virus. Lancet Infect Dis. 2010;10:643-651.
52. Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, et al. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. J Peripher Nerv Syst. 2009;14:310-315.
53. Baxter R, Lewis N, Bakshi N, et al. Recurrent Guillain-Barré syndrome following vaccination. Clin Infect Dis. 2012;54:800-804.
54. US Centers for Disease Control and Prevention. Guillain-Barré syndrome and vaccines 2020. https://www.cdc.gov/vaccinesafety/concerns/guillain-barre-syndrome.html. Accessed December 30, 2020.
55. Doneddu PE, Bianchi E, Cocito D, et al. Risk factors for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): ante-ceded events, lifestyle and dietary habits. Data from the Italian CIDP database. Eur J Neurol. 2020;27:136-143.
56. Pritchard J, Mukherjee R, Hughes RA. Risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation. J Neurol Neurosurg Psychiatry. 2002;73:348-349.
57. Shinjo SK, de Moraes JC, Levy-Neto M, et al. Pandemic unadjuvanted influenza a (H1N1) vaccine in dermatomyositis and polymyositis: immunogenicity independent of therapy and no harmful effect in disease. Vaccine. 2012;31:202-206.
58. Stubgen JP. A review on the association between inflammatory myopathies and vaccination. Autoimmun Rev. 2014;13:31-39.
59. World Health Organization. Weekly epidemiological update-December 29. https://www.who.int/publications/m/item/weekly-epidemiological-update-29-december-2020. Accessed December 30, 2020.
60. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579:265-269.
61. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5:562-569.
62. Ye Y, Hogue BG. Role of the coronavirus E viroporin protein binding domain of the SARS CoV nucleocapsid protein. J Virol. 2007;81:3597-3607.
63. Neuman BW, Adair BD, Yoshioka C, et al. Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. J Virol. 2006;80:7918-7928.
64. Huang Q, Yu L, Petsos AM, et al. Structure of the N-terminal RNA-binding domain of the SARS-CoV nucleocapsid protein. Biochemistry. 2004;43:6059-6063.
65. World Health Organization. SARS-CoV2 new variants: https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/. Accessed January 7, 2021.
66. US Centers for Disease Control and Prevention. SARS-CoV2 new variants. https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-emerging-variant.html. Accessed January 7, 2021.
67. Machii J, Herskovitz J, Sena AM, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. J Neuroimmune Pharmacol. 2020;15:359-386.

68. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683-690.

69. Uncini A, Vallat JM, Jacobs BC. Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. J Neurol Neurosurg Psychiatry. 2020;91:1105-1110.

70. Dalakas MC. Guillain-Barré syndrome: the first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing. Neurol Neuroimmunol Neuroinflammation. 2020;7:e781.

71. Fantini J, Di Scala C, Chahinian H, et al. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents. 2020;55:105960.

72. Bagnato S, Boccagni C, Marino G, et al. Critical illness myopathy and mononeuritis multiplex: clinical and experimental correlates. Eur J Neurol. 2020;27:50-51.

73. Machhi J, Herskovitz J, Sena AM, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. J Neuroimmune Pharmacol. 2020;15:359-386.
103. US Centers for Disease Control and Prevention. Ensuring the safety of COVID-19 vaccines in the United States 2020 [updated December 22, 2020]. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety.html. Accessed December 30, 2020.

104. US Centers for Disease Control and Prevention. Live and inactivated vaccines. https://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Accessed December 30, 2020.

105. US Centers for Disease Control and Prevention. Adult immunization schedule. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Accessed December 30, 2020.

APPENDIX: AANEM QUALITY AND PATIENT SAFETY COMMITTEE MEMBERS 2020

Pushpa Narayanaswami MBBS, DM (Chair); Michele L. Arnold MD; David R. Del Toro MD; Urvi G. Desai MD; Nida G. Gleveckas-Martens DO; Gregory Gruener MD, MBA, MHBE; Lyell K. Jones MD; Charles D. Kassardjian MD, MSc; John C. Kincaid MD; Michelle Aldonsa McFarlane MD; Earnest L. Murray MD; Jayashri Srinivasan MBBS, PhD; Deborah A. Venesy MD; Sasha A. Živković MD, PhD.

How to cite this article: Živković SA, Gruener G, Narayanaswami P, the AANEM Quality and Patient Safety Committee. Doctor—Should I get the COVID-19 vaccine? Infection and immunization in individuals with neuromuscular disorders. Muscle & Nerve. 2021:63:294–303. https://doi.org/10.1002/mus.27179