Clinical Guidance on COVID-19 Vaccines for People with Autoimmune Neuromuscular Disorders Receiving Immunosuppressive/ Immunomodulating Therapy

This guidance is intended for health-care providers and is based on known evidence as of June 17 2021.

Background and Context

- Some patients with significant autoimmune/inflammatory diseases of the neurologic system (including the brain, spinal cord, motor nerves, neuromuscular junction and muscles – referred to broadly as neuromuscular) require treatment with immunotherapies. [1]
- These diseases (including multiple sclerosis, neuromyelitis optica, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, and inflammatory myopathy) result from immune tolerance dysfunction such that the patient's immune system attacks their own tissues.
- Patients with neuromuscular conditions who require treatment with immunosuppressive medications are at increased risk of hospitalization and mortality from COVID-19. [2]

This guidance is based on a review of three of the vaccines approved by Health Canada for the prevention of COVID-19 disease caused by the SARS-CoV-2 virus: Pfizer-BioNTech (BNT162b2)[3] and Moderna (mRNA-1273)[4], which are mRNA vaccines, and AstraZeneca/COVISHIELD (ChADOx1-S)[5] which is a replication-defective-adenoviral-vector ('viral vector') vaccine.

Currently, anyone aged 12+ (born in 2009 and earlier) in British Columbia is eligible for COVID-19 immunization. At this time, only the Pfizer-BioNTech mRNA vaccine is authorized for youth aged 12-17,[3] and we are expecting that Health Canada will authorize the Moderna mRNA vaccine for 12-17 year olds in the near future. Studies of the COVID-19 vaccines in younger children are ongoing.

As per the National Advisory Committee on Immunization (NACI), the two mRNA vaccines authorized in Canada (Pfizer-BioNTech and Moderna) can be interchanged for the second dose to complete the series, if the vaccine received for the first dose is not available or is unknown. No data currently exist on the interchangeability of the COVID-19 mRNA vaccines. However, there is no reason to believe that mRNA vaccine series completion with a different authorized mRNA

-

vaccine product will result in any additional safety issues of deficiency in protection. You should not receive an AstraZeneca vaccine for your second dose.

The AstraZeneca/COVISHIELD COVID-19 vaccine program has been stopped in B.C. for first doses, unless there is a contraindication to the mRNA vaccines, or as advised by the Medical Health Officer or an allergist, due to rare (1:100,000) but serious Vaccine-Induced Thrombotic Thrombocytopenia (VITT) blood clotting events and the large supply of other vaccines without this safety concern. The risk of VITT is six times lower for the second dose (1:600,000). People who received the AstraZeneca/COVISHIELD vaccine for their first dose have the option of receiving AstraZeneca/COVISHIELD or an mRNA vaccine for their second dose. Receiving a mixed vaccine series (AstraZeneca/COVISHIELD for first dose and an mRNA vaccine for the second dose) is permitted based on small studies that suggest that this is likely safe and likely as effective and may be even more effective, but not enough is known to make firm conclusions and data collection is ongoing. There may also be heightened side effects experienced with a mixed vaccine series. The BCCDC has prepared two information sheets to help navigate that choice:

> **For health care professionals**: www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Immunization/Vaccine%20Info/COVID-19-vaccine-second-dose-considerations-HCP-QandA.pdf
>
> **For patients**: www.bccdc.ca/Health-Info-Site/Documents/COVID-19_vaccine/AstraZeneca_2ndDose.pdf

Another viral vector vaccine, Janssen/Johnson & Johnson (Ad26.COV2.S), has been approved by Health Canada but will not be part of BC's COVID-19 immunization program at this time. As well, another emerging vaccine candidate developed by Novavax may also be approved by Health Canada in the coming months. This vaccine works differently than the approved vaccines in Canada. This guidance will be updated as more information becomes available.

The current interval between doses observed in British Columbia for the general public is 8 weeks. For individuals who have been designated by the Ministry of Health as Clinically Extremely Vulnerable (CEV), as of June 3rd 2021, the dose interval is in line with the manufacturer's recommended dosing interval (21 days for Pfizer-BioNTech, 28 days for Moderna, 8-12 weeks for AstraZeneca/COVISHIELD).

People were generally excluded from the Pfizer-BioNTech and Moderna COVID-19 vaccine trials if they were on immunosuppressant treatment. Therefore, there are still uncertainties as to whether COVID-19 vaccine is efficacious and safe in patients with autoimmune neuromuscular disorders on therapy, as well as to the timing of immunization in relation to their treatments. [7,1]

Is COVID-19 immunization recommended for patients with neuromuscular disorders receiving immunosuppressive/immunomodulating therapy?

COVID-19 immunization is not contraindicated and should be encouraged for patients with neuromuscular disorders receiving immunosuppressive/immunomodulating therapy, including those who have had COVID-19 infection. This recommendation is based on the following review:

- The National Advisory Committee on Immunization recommends that immunosuppressed individuals may be offered the vaccine if the benefits of vaccine outweigh the potential risks.[8]
- Based on the GBS/CIDP Foundation Global Medical Advisory Board's statement on January 21, 2021: "Neither the Centers for Disease Control and Prevention (CDC) nor the Food and Drug Administration (FDA) recommends against administration of the COVID-19 vaccine in patients with chronic inflammatory demyelinating polyneuropathy or multifocal motor neuropathy … Even though there is no long-term data yet, there is no scientific reason to think that the vaccine will cause problems in those patients with CIDP or MMN."[9]
- Based on the statement from the National Multiple Sclerosis (MS) Advisory Board/The Canadian Network of Multiple Sclerosis Clinics Statement on February 10, 2021: "Most people with relapsing and progressive forms of MS should be vaccinated. The risks of COVID-19 disease outweigh any potential risks from the vaccine…The vaccines are not likely to trigger an MS relapse or to worsen your chronic MS symptoms. The risk of getting COVID-19 far outweighs any risk of having an MS relapse from the vaccine."[10]

While data specific to the safety and efficacy of the Pfizer and Moderna COVID-19 vaccines in people who take immunosuppressant or immunomodulating therapies is currently limited, the authors of this guidance agree that the benefits of vaccine-induced immunity against COVID-19 for this population outweigh any theoretical risks of immunization.

The risks of COVID-19 infection to neuromuscular patients treated with immunotherapy include the following factors:

- During the COVID-19 pandemic, patients with neuromuscular disorders may be at greater risk of worse outcomes than otherwise healthy people because of an immunocompromised state related to immunotherapy. Immunosuppressive therapies can limit immune competence.[11]This can affect the risk of infections[12]; some therapies are associated with an increased risk from particular types of pathogens.
  - Patients with autoimmune neuromuscular disorders (such as myasthenia gravis) who are infected with SARS-CoV-2 are frequently admitted to hospitals, have disease exacerbations and a higher mortality than the general population with COVID-19.[13]
  - Patients must continue with immunotherapy to avoid increasing symptoms including weakness of respiratory and bulbar muscles; the risk of relapse may result in permanent disability.
- Infections are a well-recognised trigger of symptom exacerbation in autoimmune conditions such as myasthenia gravis and multiple sclerosis.[14]
- Individual considerations regarding the appropriateness of the vaccine in patients with neuromuscular disease include, but are not limited to:
  - Level of activity of virus in the patient's local community
  - Individual risk of severe disease or death in patient contracting SARS-CoV-2 due to their neuromuscular condition and independent of their neuromuscular diagnosis (e.g., age and other comorbidities)
  - Whether family, care providers, and close contacts of the patient can receive immunization if they have no contraindication

Is COVID-19 immunization efficacious and safe for patients with neuromuscular disorders receiving immunosuppressive/immunomodulating therapy?

- Individuals with neuromuscular diseases who are treated with immunosuppressant therapy and immunosuppressed people in general were excluded in phase 3 studies of COVID-19 vaccines.[3, 4,5]
- As per NACI, safety data in immunocompromised individuals, including those receiving immunosuppressive therapy, were available from observational studies in people who were taking immunosuppressive therapies. The frequency and severity of adverse events following vaccination with an mRNA COVID-19 vaccine were comparable to that of non-immunocompromised individuals in these studies and what was reported in clinical trials. Safety data in these populations following vaccination with a viral vector vaccine is not available.
- Informed consent should include discussion about the possibility that individuals who are immunosuppressed may have a diminished immune response to any of the authorized COVID-19 vaccines, as well as a discussion about the emerging evidence on the safety of mRNA COVID-19 vaccines in these populations. The recommendations in this clinical guidance are based on these small observational studies, extrapolation of data from other viral infections, immunology of immunizations and from expert opinion.
- There is limited information on the effectiveness of vaccines in individuals who are on immunosuppressive medications. [7] However, even reduced efficacy may confer benefits against COVID-19 infections. [1]
- As immune response to COVID-19 immunization is unknown for those taking immunosuppressant or immunomodulating therapy, patients with neuroimmunological disease who receive the COVID-19 vaccine should continue to closely follow public health recommendations including social distancing, regular hand washing and/or disinfection.
- An increased risk of developing autoimmune or inflammatory disorders was not observed in clinical trial participants who received an mRNA COVID-19 immunization compared to placebo. There is no data regarding the risk of exacerbation of autoimmune neuromuscular disorders by the mRNA COVID-19 vaccines.[1]

Are there any specific contraindications or exceptions for patients with neuromuscular disorders receiving immunosuppressive/immunomodulating therapy?

Allergy to vaccine components

Individuals should not receive the vaccines if they have a history of severe allergic reaction to a previous dose of the respective vaccine or any component of the vaccines.[8] For a list of components in the vaccine and packaging consult the respective COVID-19 mRNA
vaccine product monographs found at:

- Pfizer BioNTech: https://covid-vaccine.canada.ca/info/pdf/pfizer-biontech-covid-19-vaccine-pm1-en.pdf
- Moderna: https://covid-vaccine.canada.ca/info/pdf/covid-19-vaccine-moderna-pm-en.pdf
- AstraZeneca: https://covid-vaccine.canada.ca/info/pdf/astrazeneca-covid-19-vaccine-pm-en.pdf and COVISHIELD: https://covid-vaccine.canada.ca/info/pdf/covishield-pm-en.pdf

People with a history of anaphylaxis without known or obvious cause, and those with suspected hypersensitivity or non-anaphylactic allergy to COVID-19 vaccine components, are advised to consult with an allergist prior to immunization. Health-care providers with patients with a history of severe allergic reactions should refer to the product monographs above to review the full ingredient list. Potential allergens that are known to cause type 1 hypersensitivities in the mRNA vaccines include polyethylene glycol (PEG).

Health Canada continues to monitor any adverse events following immunization through their post-authorization surveillance process.

Guillain Barre Syndrome (GBS)

Individuals with a history of GBS may receive COVID-19 mRNA vaccines unless they have other contraindications to vaccination.

- No instances of GBS were seen during clinical trials of the Pfizer and Moderna mRNA vaccines [3,4], and neither the U.S. Centers for Disease Control and Prevention (CDC) nor the Food and Drug Administration (FDA) recommends against the vaccine due to GBS. [15]
- The incidence of GBS in the United Kingdom decreased by 50% during the first wave of COVID-19, likely due to COVID-19 control measures put in place which reduced the incidence of viral infection generally, compared to the same period during the four years prior. [16]
- An analysis of the genetic and protein structure of SARS-CoV-2 showed that it contains no additional immunogenic material known or proven to drive an immune response that would trigger GBS. [17]

Bell's palsy

Cases of Bell's palsy were reported in participants in the mRNA COVID-19 vaccine clinical trials. However, there was not an excess of Bell's palsy in the COVID-19 vaccine arm and the FDA does not consider these to be above the rate expected in the general population. They have not concluded these cases were caused by immunization. Therefore, the U.S. CDC recommends that individuals who have previously had Bell's Palsy may receive an mRNA COVID-19 vaccine. [15]

Multiple Sclerosis

Systematic reviews have not shown that vaccines cause or worsen multiple sclerosis. [18]

Other vaccinations

COVID-19 vaccines can be given concomitantly with, or any time before or after any other live or inactivated vaccine. This is a change from the previous recommendation for a 14-day interval before or after receipt of a COVID-19 vaccine. The original advice against co-administration was based on a cautionary approach, as specific studies of co-administration with other vaccines have not been performed. However, substantial data have now been collected regarding the safety of COVID-19 vaccines currently authorized by Health Canada. Extensive experience with non-COVID-19 vaccines has demonstrated that immunogenicity and adverse event profiles are generally similar when vaccines are administered simultaneously as when they are administered alone. The basis for this change in recommendation is

referenced to general administrative guidance for vaccines and guidance from the US Advisory Committee on Immunization Practice (ACIP).

Are there specific recommendations or considerations for safe and/or most effective vaccine administration?

Aligned with the Canadian Rheumatology Association's guidelines. [19] , our recommendations are:

1) For patients on the following medications, there is **no need** to adjust or delay the medication:
    - **Hydroxychloroquine,**
    - **Prednisone less than 20mg/day,**
    - **IVIg**[20]
    - **Sulfasalazine,**
    - **Teriflunamide leflunomide,**
    - **Azathioprine,**
    - **Oral cyclophosphamide ,**
    - **Tacrolimus tocilizumab,**
    - **Cyclosporin, interferons,**
    - **Glatiramer acetate,**
    - **Dimethyl fumerate,**
    - **Natalizumab.**
2) For patients on the following medications, there are two options:
    a) Do not change medication dosing or
    b) Adjust medication dosing to optimize the immune response to the vaccine:
        i. For patients on weekly **methotrexate**, an option is to skip the methotrexate dose the following week after each vaccine dose.
        ii. For patients on intravenous **cyclophosphamide**, an option is to take each vaccine dose at least one week prior to the next cyclophosphamide infusion.
        iii. For patients on **rituximab** or **ocrelizumab**, the COVID-19 vaccination should ideally be timed four to five months after their last infusion and two to four weeks prior to their next infusion, when possible, in order to optimize vaccine response. However, in patients who require immediate infusion or who are unable to optimize timing of infusion product and vaccine, it is likely more important to have the COVID-19 vaccine earlier than to delay based on timing of B-cell therapy
        iv. For MS patients who are requiring first or repeat dosing of **cladribine** or **alemtuzumab** a delay with bridging of **Tysabri** could be considered until after full vaccine course plus four weeks. If treatment is required because of active disease, then vaccination will need to be delayed by four to six months after treatment.
        v. For patients on **mycophenolate mofetil**, if the disease is stable, the medication may be held for one week following each COVID-19 vaccine dose.
        vi. For patients on **prednisone** 20mg/d or higher, consider waiting until the prednisone dose is tapered to below 20mg/d to receive both vaccine doses. [15] (Note: for individuals with Duchenne's Muscular Dystrophy on deflazacort, Parent Project Muscular Dystrophy and Muscular Dystrophy Canada recommend vaccination on current prednisone dose) [21]

References

1. Živković, SA, Gruener, G, Narayanaswami, P, Doctor—Should I get the COVID-19 vaccine? Infection and immunization in individuals with neuromuscular disorders. *Muscle & Nerve*. 2021; 63: 294–303.
2. Korsukewitz, C., Reddel, S.W., Bar-Or, A. *et al.* Neurological immunotherapy in the era of COVID-19 — looking for consensus in the literature. *Nature Reviews Neurology. 2020;* **16,** 493–505.
3. Pfizer. Pfizer-BioNTech COVID-19 vaccine product monograph. Kirkland, Quebec. 9 December 2020.
4. Moderna. Moderna COVID-19 vaccine product monograph. Cambridge, MA, USA. 23 December 2020.
5. AstraZeneca COVID-19 vaccine product monograph. https://covid-vaccine.canada.ca/info/pdf/astrazeneca-covid-19-vaccine-pm-en.pdf Accessed: March 7, 2021.
6. Janssen COVID-19 vaccine product monograph. https://covid-vaccine.canada.ca/info/pdf/janssen-covid-19-vaccine-pm-en.pdf, Accessed: March 7, 2021
7. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clinical Infectious Diseases*. 2014;58:e44-e100.
8. National Advisory Committee on Immunization. Recommendations on the use of COVID-19 vaccine(s). 1 March 2021. Available at: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html. Accessed on: 7 March 2021.
9. GBS/CIDP Foundation International Medical Advisory Board statement on COVID vaccines for CIDP and MMN. 21 January, 2021. Available at: https://www.gbs-cidp.org/2021/01/21/foundation-global-medical-advisory-board-statement-on-covid-vaccines-for-cidp-and-mmn. Accessed on 15 February 2021.
10. MS Society of Canada's Medical Advisory Committee statement on CO ID-19 Vaccine Guidance for People Living with MS. 10 February, 2021. https://mssociety.ca/resources/news/article/covid-19-vaccine-guidance-for-people-living-with-ms. Accessed on 15 February 2021.
11. Kovarik, J. From immunosuppression to immunomodulation: current principles and future strategies. *Pathobiology*. 2013; 80, 275–281.
12. Willis, M. D. & Robertson, N. P. Multiple sclerosis and the risk of infection: considerations in the threat of the novel coronavirus, COVID-19/SARS-CoV-2. *Journal of Neurology*. 2020; 267, 1567–1569.
13. Wu, Z., McGoogan, J. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Journal of the American Medical Association.* 2020; **323**: 1239-1242.
14. Loebermann M, Winkelmann A, Hartung HP, Hengel H, Reisinger EC, Zettl UK. Vaccination against infection in patients with multiple sclerosis. *Nat Rev Neurol*. 2012 Jan 24;8(3):143-51.
15. Vaccine Considerations for People with Underlying Medical Conditions. 29 December, 2020. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/underlying-conditions.html. Accessed on 15 February 2021.
16. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain* 2020;awaa433.
17. Hurley, D. No Excess Risk for Neurologic Events Observed to Date from COVID-19 Vaccines. Neurotodayonliine Blog. 15 January 2021 https://journals.lww.com/neurotodayonline/blog/breakingnews/pages/post.aspx?PostID=1075 Accessed on 15 February 2021.
18. Zrzavy et al. Vaccination in Multiple Sclerosis: Friend or Foe? *Front Immunol* 2019;10:1883

19. American College of Rheumatology Covid-19 Vaccine Clinical Guidance Summary for patients with Rheumatic Disease. February 8, 2021
20. US Centers for Disease Control and Prevention, Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html Accessed 11 March 2021
21. Muscular Dystrophy Canada https://muscle.ca/covid-19/ask-the-experts Accessed 16 February 2021

Authors

Dr. Kristine Chapman, Division of Neurology, Department of Medicine, University of British Columbia

Mary Nieforth, Operations Director, Vancouver Acute, Vancouver Coastal Health

Dr. Hannah Briemberg, Division of Neurology, Department of Medicine, University of British Columbia

Dr. Virginia Devonshire, Division of Neurology, Department of Medicine, University of British Columbia

Dr. Yahya Agha-Khani, Division of Neurology, Department of Medicine, University of British Columbia

Dr. Andrea Townsend, Division of Physical Medicine and Rehabilitation, Department of Medicine, University of British Columbia

Dr. Jennifer Yao, Division of Physical Medicine and Rehabilitation, Department of Medicine, University of British Columbia

Dr. Kathryn Selby, Division of Neurology, Department of Pediatrics, University of British Columbia

Dr. Jeremy Road, Division of Respiratory Medicine, Department of Medicine, University of British Columbia

Dr. Marie Wright, Division of Respiratory Medicine, Department of Pediatrics, University of British Columbia