Clinical Guidance on COVID-19 Vaccines for People with Paroxysmal Nocturnal Hemoglobinuria and Atypical Hemolytic Uremic Syndrome

This guidance is intended for health-care providers. It is based on known evidence as of June 16, 2021.

Background and Context

This document provides guidance for COVID-19 immunization in patients with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS).

This guidance is based on a review of the safety and efficacy data of three of the current Health Canada approved vaccines for the prevention of COVID-19 disease caused by the SARS-CoV-2 virus: Pfizer-BioNTech (BNT162b2)[1] and Moderna (mRNA-1273)[2], both of which are mRNA vaccines, as well as AstraZeneca/COVISHIELD (ChADOx1-S)[3] which is a replication defective adenoviral vector vaccine.

Currently, anyone aged 12+ (born in 2009 and later) 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.

The AstraZeneca/COVISHIELD COVID-19 vaccine program has been stopped in B.C. for first doses, due to rare (1:50,000) 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

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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/COVIDSHIELD).

PNH is a rare, acquired disorder of complement mediated red cell hemolysis associated with a very high chance of thrombosis and, sometimes, neutropenia from associated bone marrow failure. Although data is very limited[6,7] on the impact of COVID-19 on PNH, rare thrombotic complications have been described[8] suggesting that there may be additional chance of severe complications from COVID-19 if PNH patients contract the virus. In addition, other viral infections are well recognized triggers for episodes of hemolysis in PNH which can have life-threatening consequences.

aHUS is a rare kidney disease related to microangiopathy. Although no data has been published on the susceptibility to and impact of COVID-19 on people with aHUS, there are numerous reports of aHUS being triggered in genetically susceptible patients by viral infections including influenza.[9] Also, COVID-19 is more likely to be severe in patients with kidney diseases[6] and renal involvement is a cardinal feature of aHUS. Crises in aHUS patients can be life-threatening with acute kidney injury and both thrombotic and hemorrhagic complications.

Is COVID-19 immunization recommended for people with PNH and aHUS?

COVID-19 vaccines are not contraindicated and should be encouraged for patients with with PNH and aHUS, including those who have had COVID-19 infection. This recommendation is based on the following review:

- PNH and aHUS are both thromboinflammatory disorders and this pathophysiology overlaps with the cytokine storm environment which characterizes severe COVID-19.[10] This shared pathophysiology does raise concerns that patients with PNH and aHUS will be more at risk of severe COVID-19 regardless of treatment status for PNH and aHUS.
- PNH and aHUS are both treated with drugs targeting the complement cascade, like eculizumab. While eculizumab may not have a direct negative effect on COVID-19,[11] severe complications of the underlying PNH or

aHUS condition in patients receiving eculizumab have been reported when they contracted COVID-19.[7,12] Also, eculizumab mediated complement blockade leads to an increased risk of some infections and, in particular, *N*eisseria infections, leading to mandatory meningococcal immunization for treated patients. [13]

- Agreement among professional societies recommending that aHUS and PNH patients receive COVID-19 immunizations. [14,15,16]

While data specific to the safety and efficacy of the Pfizer-BioNTech, Moderna, and AstraZeneca/COVISHIELD COVID-19 vaccines for people with PNH and aHUS 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.

Is COVID-19 immunization efficacious and safe for people with PNH and aHUS?

As both PNH and aHUS are considered to be severe underlying medical diseases, they would have been excluded from the Pfizer-BioNTech, Moderna, and AstraZeneca COVID-19 vaccine clinical trials. Therefore, it is unknown if the currently available COVID-19 vaccines are as efficacious for patients with PNH and aHUS as they were found to be for the trial population.

Vaccine efficacy may theoretically be reduced in patients with PNH who have been treated with anti-thymocyte globulin for aplastic anemia in the six months prior to receiving the vaccine. [15] It is expected that this consideration may apply to only a very small number of patients in the province, and the patient's hematologist should inform the patient taking this treatment that the vaccine may not provide optimum protection.

Otherwise, there is nothing from a disease perspective pertinent to PNH and aHUS to suggest that the vaccines would be less efficacious or safe for people with PNH and aHUS than they are for the general population. The Pfizer-BioNTech and Moderna mRNA vaccines are not live vaccines, and the AstraZeneca vaccine is a replication-defective adenovirus vaccine. Thus, they do not pose a risk to PNH and aHUS patients. The benefits of immunization are expected to be similar to that of the general population.

Are there any specific contraindications or exceptions for patients with PNH and aHUS?

Individuals should not receive a COVID-19 vaccine if they have a history of severe allergic reaction to a previous dose of the respective vaccine or any component of the vaccines.[4] For a list of components in the vaccine and packaging consult the respective COVID-19 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) in the mRNA vaccines and Polysorbate 80 in the viral vector vaccine.

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

COVID-19 vaccines can be given concomitantly with, or any time before or after any other indicated 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).

Other than allergy and the safety and efficacy considerations described above, and the medication timing considerations described below, and there are no specific contraindications or exceptions for people with PNH and aHUS.

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

Patients who are on eculizumab should time their vaccination so it occurs as close as possible to their dose (within days before or days after their dose) due to the theoretical possibility that this may reduce their chance of having exacerbation of their disease related to vaccine administration. Typical eculizumab dosing intervals are biweekly.

Some patients with these disorders may be thrombocytopenic or on anticoagulation medication. Guidance developed for the general population who may be on anticoagulants (e.g., prolonged pressure at the site, etc.) can also be applied to those members of this population as they are at increased bleeding risk.

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