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

This guidance is intended for healthcare providers. It is based on known evidence as of November 8, 2022.

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 vaccines approved by Health Canada for the prevention of COVID-19 disease caused by the SARS-CoV-2 virus:

- **mRNA vaccines**: tozinameran (COMIRNATY, Pfizer-BioNTech),\(^1\) tozinameran and riltozinameran (COMIRNATY Bivalent original & BA.1, Pfizer-BioNTech),\(^2\) tozinameran and famtozinameran (COMIRNATY Bivalent original & BA.4/BA.4, Pfizer-BioNTech),\(^3\) elasomeran (SPIKEVAX, Moderna),\(^4\) elasomeran and imelasomeran (SPIKEVAX Bivalent original & BA.1, Moderna)\(^5\)
- **Viral vector vaccine**: ChADOx1-S (VAXZEVRIA, AstraZeneca),\(^6\) Ad26.COV2.S (JCVODEN, Janssen)\(^7\)
- **Recombinant protein vaccine**: COVID-19 Vaccine (recombinant protein, adjuvanted) (NUVAXOVID, Novavax)\(^8\)
- **Plant based virus-like particle (VLP) vaccine**: COVID-19 Vaccine ([VLP], recombinant, adjuvanted) (COVIFENZ, Medicago)\(^9\)

Currently, anyone in British Columbia (B.C.) who is aged 6 months and older is eligible for COVID-19 immunization. The mRNA vaccine SPIKEVAX (Moderna) and COMIRNATY (Pfizer-BioNTech) have been approved for children 6 months to 11 years of age, with young children getting a smaller dose of the same vaccine used for youth and adults.\(^10\) National Advisory Committee on Immunization (NACI) has released their statement for these age groups.\(^11,12,13\)

People who receive the mRNA vaccine (COMIRNATY [Pfizer-BioNTech] or SPIKEVAX [Moderna]) for their first dose, will be offered either mRNA vaccine for subsequent doses, with the exception of preferential recommendations based on age and immunosuppression.\(^14,15\) B.C. has taken the proactive step to expand booster doses for all individuals 5 years and older, not just those at high risk. However, it is particularly recommended for individuals 5-17 years of age who are at [higher risk of severe illness](#) due to COVID-19 infection.\(^16,17\) All booster doses will be mRNA vaccines.\(^18\) For those who
are not able, or willing, to receive mRNA vaccines, Novavax is available as an alternative for individuals 18 years of age and older.

**Booster doses:**

As part of the Fall 2022 booster dose program, B.C. is making plans to offer everyone 5 years and older a booster dose. NACI has been clear this approach will provide the best protection in the Fall and Winter when we’re all spending more time inside and respiratory illness is passed around our communities.¹⁹

SPIKEVAX BIVALENT BA.1 (Moderna) (50 mcg) is the preferred product in B.C. for moderately to severely immunosuppressed individuals 12 years and older. SPIKEVAX original (Moderna) (100 mcg) primary series has been associated with a higher seroconversion rate among immunocompromised adult patients compared to COMIRNATY original (Pfizer-BioNTech) (30 mcg). In a general population of adults, booster vaccination with SPIKEVAX original (Moderna) (50 mcg) was also found to be more effective than COMIRNATY original (Pfizer-BioNTech) (30 mcg) during a period of Delta followed by Omicron variant dominance. However, these studies were conducted prior to the emergence of the Omicron BA.4/BA.5 Variant of Concern (VOC), and their applicability to all Omicron sublineages is uncertain.¹⁹ Health Canada has recently authorized an adapted version of the SPIKEVAX (Moderna) COVID-19 vaccine that targets the Omicron BA.4/BA.5 subvariants.²⁰

**Patients who have tested positive for COVID-19:**

Booster doses may be deferred in those who have tested positive for COVID-19 until 3-6 months from symptom onset or, for asymptomatic cases, from the time of the positive test.²¹ This suggested interval is based on immunological principles and expert opinion. When considering whether or not to administer vaccine doses following the suggested 3–6-month interval, biological and social risk factors for exposure (e.g., local epidemiology, circulation of VOCs, living settings) and severe disease should also be taken into account. As these intervals are to be used as a guide, clinical discretion is advised.

COVID-19 vaccination may be offered to individuals at any time following recovery from SARS-CoV-2 infection.

**Intervals between doses:**

Individuals requesting a shorter interval between doses should be informed that this actually offers less optimal protection, but their request for an earlier dose should be granted, without need for Medical Health Officer approval, provided the minimum interval between doses has been observed.²²

The minimum interval between completion of the primary series, or a previous booster dose, and the Fall booster dose is 3 months. This revised minimum interval additionally applies to pregnant people and aligns with NACI’s updated guidance on COVID-19 vaccines for individuals who are pregnant or breastfeeding. The exception to this is JCVODEN (Janssen) for which the minimum interval is 8 weeks between the single dose of JCVODEN (Janssen) and the booster dose.²³
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Other vaccines:

**VAXZEVRIA (AstraZeneca)**

The VAXZEVRIA (AstraZeneca) 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 infrequent but serious Vaccine-Induced Thrombotic Thrombocytopenia (VITT) blood clotting events after the first dose. The Government of Canada is not securing additional VAXZEVRIA doses.

**JCVODEN (Janssen)**

The JCVODEN one-dose viral vector vaccine is now available in limited supply in B.C. However, mRNA vaccines are preferred over viral vector vaccines due to better effectiveness and immunogenicity of mRNA vaccines and the possible adverse effects specifically associated with viral vector vaccines (e.g., Thrombosis and Thrombocytopenia Syndrome [TTS]). A viral vector COVID-19 vaccine should only be considered when all other authorized COVID-19 vaccines are contraindicated or have been refused, due to the reduced effectiveness and the possible adverse effects associated with viral vector vaccines (e.g., TTS).

**NUVAXOVID (Novavax)**

NUVAXOVID is a different class of vaccination, a protein subunit vaccine that will give British Columbians another option to protect themselves against COVID-19 infection. NUVAXOVID may be offered to individuals for whom COVID-19 mRNA vaccines are contraindicated or have been refused. This vaccine is available to people aged 18 years and older. It is a two-dose vaccine and a limited number of doses will be available in B.C.

**COVIFENZ (Medicago)**

COVIFENZ is a different class of vaccination, a plant-based virus-like particle vaccine that will give British Columbians another option to protect themselves against COVID-19 infection. COVIFENZ is approved for people who are 18 to 64 years of age. It is a two-dose vaccine and a limited number of doses will be available in B.C. This product is not yet available in Canada.

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 on the impact of COVID-19 on PNH, rare thrombotic complications have been described 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. Also, COVID-19 is more likely to be severe in patients with kidney diseases 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 should be encouraged for patients with PNH and aHUS and are not contraindicated, 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. 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, severe complications of the underlying PNH or aHUS condition in patients receiving eculizumab have been reported when they contracted COVID-19. Also, eculizumab mediated complement blockade leads to an increased risk of some infections and, in particular, Neisseria infections, leading to mandatory meningococcal immunization for treated patients.
- Agreement among professional societies recommending that aHUS and PNH patients receive COVID-19 immunizations.

While data specific to the safety and efficacy of the COMIRNATY (Pfizer-BioNTech), SPIKEVAX (Moderna), and VAXZEVRIA (AstraZeneca) vaccines for people with PNH and aHUS is currently limited, there are data to suggest that the currently available COVID-19 vaccines have efficacy. 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 COMIRNATY (Pfizer-BioNTech), SPIKEVAX (Moderna) and VAXZEVRIA (AstraZeneca) 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. 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 mRNA vaccines (COMIRNATY (Pfizer-BioNTech), SPIKEVAX (Moderna) are not live vaccines, and the VAXZEVRIA (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 who have had a severe allergic reaction to an ingredient of one type of COVID-19 vaccine are still able to receive future doses of the other type of vaccine. BCCDC has a list of the individual components and their purpose in the vaccines. For a complete list of components in the vaccine, consult the vaccine monographs found at: www.bccdc.ca/health-info/diseases-conditions/covid-19/covid-19-vaccine/vaccines-for-covid-19.

For individuals with a history of anaphylactic reaction to a previous dose of an mRNA COVID-19 vaccine, re-vaccination (i.e., administration of a subsequent dose in the series when indicated) may be offered with the same vaccine or the same mRNA platform if a risk assessment deems that the benefits outweigh the potential risks for the individual and if informed consent is provided. Prior to revaccination, consultation with an allergist or another appropriate physician (e.g., Medical Health Officer) is advised. If re-vaccination is going ahead, vaccine administration should be done in a controlled setting with expertise and equipment to manage anaphylaxis, with an extended period of observation of at least 30 minutes after re-vaccination.

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.

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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37. [https://www.atypicalhus.co.uk/](https://www.atypicalhus.co.uk/)


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