Clinical Guidance on COVID-19 Vaccines for People with Metabolically Unstable Inborn Errors of Metabolism

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

Background and Context

This document provides COVID-19 vaccine guidance for adults and children with metabolically unstable inborn errors of metabolism (IEM) including: urea cycle defects, methylmalonic aciduria, propionic acidemia, glutaric aciduria, and maple syrup urine disease. Patients with other rare IEM may also be determined to be metabolically unstable by British Columbia adult and pediatric experts.

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 ('viral 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 and above,[1] 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)[4]. 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

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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).

Is COVID-19 immunization recommended for people with metabolically unstable inborn errors of metabolism?

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

- IEM may place a patient at increased risk of complications if they develop intercurrent illness including COVID-19. No data have been published addressing the impact of COVID-19 on most of these disorders; however, a single case report[6] documents that COVID-19 can be a trigger for metabolic decompensation as other viral and bacterial infections.
- Infection may lead to severe complications including metabolic stroke and this phenomenon is well-documented in other viruses including influenza.[7]
- Although data are sparse on immune function in these rare conditions, one study did suggest that some patients with IEM are more prone to unusual infections, which suggests a suppressive effect of the condition on global immune function.[8]
- Metabolic decompensation is very rapid and patients can progress from being well to critical state in a matter of hours. The consequences of metabolic decompensation in these disorders are severe and include cerebral edema, coma and death.
- Also, some of the disorders may be associated with chronic kidney disease which puts the patients at higher risk of severe disease and mortality from COVID-19[9].
- The European Reference Network recommends that patients with IEM should be immunized against COVID-19.[10]

While data specific to the safety and efficacy of COVID-19 vaccines for people with inborn errors of metabolism 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 metabolically unstable inborn errors of metabolism?

As IEM are considered to be severe underlying medical diseases, people with these conditions were excluded from the COVID-19 vaccine clinical trials. Therefore, it is unknown if the currently available COVID-19 vaccines are as efficacious for patients with IEM as they were found to be for the clinical trial participants. There is nothing from a disease or treatment perspective pertinent to IEM to suggest that the vaccines would be less efficacious or safe for people with IEM 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 and does not pose a risk of precipitating metabolic decompensation. Given that intercurrent systemic infections are a known precipitant of decompensation in patients with IEM, an event with life threatening consequences, the benefits of immunization are expected to be similar to the general population.

Are there any specific contraindications or exceptions for patients with metabolically unstable inborn errors of metabolism?

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.

Other than allergy, there are no specific contraindications or exceptions for people with IEM. 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).

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

Patients who are experiencing a disease flare-up on the day of their vaccine appointment should cancel the appointment and re-book when their condition has stabilized. No additional precautions are required for safe or effective administration in this population.

References

1. Pfizer. Pfizer-BioNTech COVID-19 vaccine product monograph. Kirkland, Quebec. 9 December 2020.
2. Moderna. Moderna COVID-19 vaccine product monograph. Cambridge, MA, USA. 23 December 2020.
3. AstraZeneca COVID-19 vaccine product monograph. https://covid-vaccine.canada.ca/info/pdf/astrazeneca-covid-19-vaccine-pm-en.pdf Accessed: March 7, 2021.
4. 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: March 1, 2021.
5. Janssen COVID-19 vaccine product monograph. https://covid-vaccine.canada.ca/info/pdf/janssen-covid-19-vaccine-pm-en.pdf, Accessed: March 7, 2021
6. Caciotti A, Procopio E, Pochiero F et al. SARS-CoV-2 infection in a patient with propionic acidemia. *Orphanet Journal of Rare Diseases*. 2020;15:3062.
7. Pena L, Champman KA, Gropman AL et al. Natural history of propionic acidemia. *Molecular Genetics and Metabolism* 202121;105:5-9.
8. Al Essa M, Rahbeeni Z, Jumaah S et al. Infections complications of propionic acidemia in Saudia Arabia. *Clinical Genetics*. 199:54:90-4.
9. Altonen BL, Arreglado TM, Leroux O et al. Characteristics, comorbidities and survival analysis of young adults hospitalized with COVID-19 in New York City. *PLoS ONE*. 2020;15:e0243343.
10. European Reference Network. *Hereditary Metabolic Disorders and COVID-19 Vaccination*. Retrieved March 2, 2021, from https://metab.ern-net.eu/wp-content/uploads/2020/07/COVID-19-Vaccine.pdf

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