Clinical Guidance on COVID- 19 Vaccines for People with Cystic Fibrosis

This guidance is intended for health-care providers. It is based on known evidence as of June 16, 2020.

Background and Context

The SARS-CoV-2 pandemic has been of particular concern for the cystic fibrosis (CF) community. CF is a multisystem condition with comorbidities that are expected to increase vulnerability to COVID-19.

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)[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,[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)[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 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

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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).

Is COVID-19 immunization recommended for people with cystic fibrosis?

All Health Canada approved COVID-19 vaccines are not contraindicated and should be encouraged for patients with CF, including those who have had COVID-19 infection. This recommendation is based on the following risk factors for patients with CF:

Chronic lung disease

Essentially all CF patients have a type of lung disease that is termed bronchiectasis. The basic defect in CF leads to chronic infection in the lungs by aggressive organisms such as pseudomonas aeruginosa that cannot be eradicated regardless of antimicrobial and other therapies.

Over time, progressive lung damage secondary to acute and chronic infection occurs, which is permanent and cumulative. This is also associated with periodic acute infection flares termed pulmonary exacerbations that require additional oral or IV antibiotic therapy.

For adult patients, the average would be two to three oral and one intravenous (IV) antibiotic courses per year. In some patients, this will be much more frequent.

This progression of lung disease accounts for the bulk of morbidity and mortality (approximately 50% of adults FEV1 <70%). The underlying complex lung disease characterized by challenging infecting organisms, is the main reason for COVID-19 vulnerability.

Other reasons for COVID-19 susceptibility

- Diabetes mellitus: Present in approximately 40% of adult CF patients (dysglycemia approximately 65%) which has been shown to be an independent factor for worse outcomes with COVID-19.
- Nutritional deficiency: Approximately 85% pancreatic insufficient with undernutrition in a substantial proportion of adults with CF.
- Chronic liver disease: Affects approximately 30% of CF patients.
- Post-transplantation: In Canada, around 1,500 CF patients have received solid organ transplants (predominantly lung) since 2019. People who have received a solid organ transplant take immunosuppressant medications, which are believed to increase risk of serious disease from COVID-19.

To date, there is very little information available to understand COVID-19 risk in people with CF. This reflects the relatively small numbers of people with CF worldwide and likely the impact of very strict infection control measures adopted by CF patients, their families and their caregivers. A recent publication based on data obtained from a number of national CF registries reported 181 patients with CF with confirmed COVID-19 infection with 11 admitted to intensive care unit (ICU) and seven deaths.[6] A more adverse outcome was reported for those of older age, concomitant diabetes, lower lung function and post transplantation status, providing direct support for the postulated comorbidities/clinical features listed above.

A risk prediction algorithm published by Clift et al,[7] based on U.K. data, included CF in a subgroup of "rare lung conditions" and reported a higher adjusted hazard ratio for hospitalization and death for both males and females.

Impact of respiratory virus in CF extrapolated from other data

CF patients commonly experience infections with a number of respiratory viruses including influenza, adenovirus, respiratory syncytial virus (RSV), enteroviruses and rhinoviruses. These infections are a common cause of pulmonary exacerbations (estimated at >50%) which drive symptom morbidity, hospitalizations, accelerate lung decline and increase mortality.

A previous meta-analysis showed 50 to 70% of CF patients testing positive for influenza A (H1N1) required hospitalization, as compared to 7 to 20% of the general population.[8] Approximately 40% of patients after an exacerbation never recover to their previous baseline.

There is every reason to implicate SARS-CoV-2 infection with similar, if not greater, adverse effects. Individuals with other chronic lung diseases also are negatively impacted by viral infections including chronic obstructive pulmonary disease, severe asthma and bronchiectasis. Although high-quality evidence is not available, influenza immunization is routinely advocated for CF patients worldwide.

Is the COVID-19 vaccine efficacious and safe for people with cystic fibrosis?

As cystic fibrosis ia considered to be a severe underlying medical condition, people with cystic fibrosis were excluded from the Pfizer-BioNTech, Moderna, and AstraZeneca COVID-19 vaccine trials. Data is currently limited as to whether COVID-19 vaccines are as efficacious for patients with cystic fibrosis as they were found to be for the clinical trial participants. However, t**here is no reason from the disease perspective that an antibody response to immunization should be attenuated.**

Cystic fibrosis transmembrane regulator mutations, which lead to CF, do not have clinically relevant impacts on the host and innate immunity. There is no evidence from other immunizations, like for influenza, of blunted immune response to immunization and this is a routine part of CF care.

CF patients are rarely on medications on a regular basis that would potentially blunt an immune reaction to immunization (e.g., oral corticosteroids or immunosuppressive therapies). If the patient has received a lung transplant, please refer to the clinical guidance for solid organ transplant recipients.

Relatively younger age of CF patients supports a robust immunological response (<5% of patients are >65 years of age).

There is no reason to assume specific safety concerns for CF patients for immunization. However, the author acknowledges there is no data directly evaluating this.

Patients with CF invariably have chronic lung disease, some severe in degree. If there was an anaphylactic reaction, there is the potential for more severe symptoms and complications. This would be similar to other patients with advanced lung disease (perhaps less so in CF as cardiovascular comorbidities would generally not be present). As such, it is recommended that health-care providers counseling patients with CF follow the allergy contra-indications and advice provided below closely, particularly for people with CF with most severe lung disease (e.g., FEV1 <40% predicted).

Are there any specific contraindications or exceptions for people with cystic fibrosis?

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 replication defective adenovirus vaccine.

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

Otherwise, there are no specific contraindications or exceptions for people with CF from a disease perspective.

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 administration?

Out of abundance of caution, it is recommended that immunization be delayed in the following circumstances:

- If the patient is currently undergoing treatment, including antibiotics for a pulmonary exacerbation of cystic fibrosis;
- If patient is hospitalized for a CF related complication like a bowel obstruction or acute pancreatitis.

Immunization delays in these circumstances would be adjudicated on an individual basis by the CF clinician.

References

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