Clinical Guidance on COVID-19 Vaccines for Persons with Autoimmune Rheumatic Diseases

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

Background and Context

The majority of adults and children with autoimmune rheumatic diseases (ARD) require immune modulating therapies for disease control. These therapies put people with ARD at higher risk for infections, particularly viral infections.[1] Immunosuppressed persons have a higher risk of poor outcomes with infections.[1, 2] Although there is limited information about outcomes for people with ARD who develop COVID-19, one international study demonstrated that prednisone and an underlying diagnosis of lupus could be associated with worse outcomes and higher mortality.[3]

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)[4], Moderna (mRNA-1273)[5], which are mRNA vaccines, and AstraZeneca/COVISHIELD (ChADOx1-S)[6] which is a replication-defective-adenoviral-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 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), 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 or 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 (1:50,000) 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 more than six times lower for the second dose (1:600,000).

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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).

Is COVID-19 immunization recommended for people with autoimmune rheumatic diseases?

COVID-19 vaccines are not contraindicated and should be encouraged for people with autoimmune rheumatic diseases, including those who have had a COVID-19 infection.

- Although the majority of patients with ARD who are immunosuppressed were excluded from clinical trials of the COVID-19 vaccines, the Canadian Rheumatology Association,[9] American College of Rheumatology[10] and British Rheumatology Association[11] have all released position statements strongly supporting the use of COVID-19 immunization in this population.
- Experts agree that the potential benefits and anticipated desirable effects of COVID-19 immunization outweigh the potential harms in persons with ARD.[9,10,11]

While data specific to the safety and efficacy of the Pfizer-BioNTech, Moderna, and AstraZeneca COVID-19 vaccines in people who take immunosuppressant or immunomodulating therapies is currently limited, the authors of this guidance agree that the benefits of COVID-19 immunization with these vaccines outweigh any theoretical risks of immunization.

Is the COVID-19 vaccine efficacious and safe in patients with autoimmune rheumatic diseases?

Adults and children with ARD who take immunosuppressant/immunomodulating therapy were excluded in all of the trials for the COVID-19 vaccines currently approved in Canada. As per NACI, safety data in immunocompromised individuals, including those receiving immunosuppressive therapies, are available from observational studies in people 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.

People with ARD can exhibit high variability with respect to clinical presentation, organ involvement, disease severity, comorbidities and medications. If a patient has complicated disease or multiple medical conditions and health-care providers have questions, they are encouraged to reach out to their specialists for specific guidance.

As the majority of patients with ARD are on immune suppressing medications, there may be blunting of the magnitude and duration of vaccine response compared to the general population.[9]

There is a theoretical risk of autoimmune rheumatic disease flare or worsening following COVID-19 immunization, which has not been previously studied or quantified. Regardless, the benefits of immunization are considered to outweigh the potential risks.

Are there any specific contraindications or exceptions for people with autoimmune rheumatic diseases?

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.[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 to review the full ingredient list. Potential allergens that are known to cause type 1 hypersensitivities in the mRNA vaccines include polyethylene glycol (PEG), and Polysorbate 80 in the replication-defective adenovirus vaccines.

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

Other than allergy, there are no specific contradictions or exceptions for people with ARD apart from the efficacy and safety considerations outlined above.

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?

Guidance from the Canadian Rheumatology Association[9] is to continue underlying immunosuppression and disease modifying agents without adjustment around COVID-19 immunization with the exception of Rituximab/Ocrelizumab, and high-dose prednisone as indicated below.

For patients on the following medications, there is **no evidence for concern around medication timing and vaccine safety. The general consensus is that no changes should be made with regards to interrupting or adjusting medication dosing around vaccination with the following:**

- **Adalimumab**
- **Anakinra**
- **Azathioprine**
- **Belimumab**
- **Canikinumab**
- **Certolizumab**
- **Cyclosporin**
- **Etanercept**
- **Golimumab**
- **Hydroxychloroquine**
- **Infliximab**
- **Intravenous immunoglobulin (IVIG)**
- **Ixekizumab**

- **Leflunomide**
- **Oral cyclophosphamide**
- **Prednisone less than 20mg/day (or equivalent)**
- **Sarilumab**
- **Secukinumab**
- **Sulfasalazine**
- **Tacrolimus**
- **Tocilizumab**
- **Ustekinumab**

For patients on **rituximab** or **ocrelizumab**, the COVID-19 immunization 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 more important to have the COVID-19 vaccine earlier than to delay based on timing of B-cell therapy.

For patients on **prednisone** 20mg/day or higher (or equivalent), consider waiting until the prednisone dose is tapered to below 20mg/d to receive both vaccine vaccine doses.

For patients receiving **methotrexate, mycophenalate mofetil, oral janus kinase inhibitors**, and **abatacept** there is emerging data that these therapies might impact ability to mount an adequate antibody response to vaccine[13,14,15,16]. Therefore, in STABLE patients, consideration can be given to holding therapy post-vaccine as described below. This is compatible with the *American College of Rheumatology*[10] recommendations which differs from the *Canadian Rheumatology Association* position statement[12].

New recommendations from the American College of Rheumatology are listed below[17]*:*

- *For patients on weekly **methotrexate (MTX)**, with well controlled disease, an option is to withhold MTX for 1-2 weeks after each vaccine dose*
- *For patients on Mycophenalate Mofetil (MMF), with stable background disease, an option is to withhold MMF for 1 week after each vaccine dose*
- *For patients on JAK inhibitors (**tofacitinib**, **baricitinib, upadacitinib)**, with well controlled disease, an option is to withhold their JAK inhibitor for 1 week after each vaccine dose.*
- *For patients on **abatacept** weekly injections, with well controlled disease, an option is to withhold the abatacept 1 week before and 1 week after the first dose of vaccine. Continue abatacept through the second dose of vaccine. For IV **abatacept**, consider timing the first dose of vaccine 4 weeks post-dose and postpone next infusion by 1 week. No IV Abatacept adjustments are needed for the second vaccine dose.*
- *For patients on **intravenous cyclophosphamide**, an option is to take each vaccine dose at least 1 week prior to the next cyclophosphamide infusion.*

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