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 March 1, 2022.

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 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),[4] elasomeran (SPIKEVAX, Moderna)[5]
- **Replication-defective adenoviral vector vaccine:** ChADOx1-S (VAXZEVRIA, AstraZeneca),[6] Ad26.COV2.S (Janssen COVID-19 Vaccine, Janssen)[7]

Currently, anyone in British Columbia who is 5 years and older is eligible for COVID-19 immunization. Health Canada has authorized COMIRNATY (Pfizer-BioNTech) vaccine made for children aged 5 to 11. NACI has released their statement for this age group[8].

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.[9,10] BC has taken the proactive step to expand booster doses for individuals 12 years and older[11] All booster doses will be mRNA vaccines.[12]

Third doses:

To date, people who are moderately to severely immunocompromised have been observed to have generally lower antibody responses and lower vaccine effectiveness from COVID-19 vaccines compared to the general population. The National Advisory Committee on Immunization[13] has reviewed this evidence and recent studies that demonstrate that some people who are immunocompromised develop an improved antibody response after a third dose of vaccine.

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As such, as of February 3, 2022, people (5 years and older) who are moderately to severely immunocompromised in B.C. are eligible to receive a third dose of an mRNA COVID-19 vaccine.[14]

A minimum interval of 28 days between dose 2 and dose 3 is recommended for those eligible for a third dose. As per the BC Immunization Manual, COMIRNATY (Pfizer-BioNTech) is recommended for those 5-11 years of age. For individuals 12 years of age and older, SPIKEVAX (Moderna) is preferred for the third dose; however, if SPIKEVAX (Moderna) is unavailable (or if the individual prefers), the COMIRNATY (Pfizer-BioNTech) vaccine may be provided.[14,15]

Specifics on current eligibility for a third dose may be reviewed here: https://www2.gov.bc.ca/gov/content/covid-19/vaccine/register#immunocompromised

Other vaccines:

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,[9] due to infrequent (1:50,000) but serious Vaccine-Induced Thrombotic Thrombocytopenia (VITT) blood clotting events after the first dose.[16] The risk of VITT is more than six times lower for the second dose (1:600,000). People who had the VAXZEVRIA (AstraZeneca) vaccine for their first dose have the option of receiving VAXZEVRIA (AstraZeneca) for their second dose, or, receiving an mRNA vaccine as their second dose. Receiving a mixed vaccine series (VAXZEVRIA (AstraZeneca) 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/Health-Info-Site/Documents/COVID-19_vaccine/Doctor_letter_Recommendations_AZ_COVISHIELD.pdf)
- **For patients**: Why your 2nd dose is important (www.bccdc.ca/Health-Info-Site/Documents/COVID-19_vaccine/AstraZeneca_2ndDose.pdf)

The Janssen COVID-19 Vaccine (Janssen)[7] 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]).

The Novavax Nuvaxoid COVID-19 vaccine was authorized for use on February 17, 2022 by Health Canada. Novavax is a different class of vaccination, a protein subunit vaccine, that will give British Columbians another option to protect themselves against COVID-19. 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. [17]

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,[18] American College of Rheumatology[19] and British Rheumatology Association[20] 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.[18-20]

While data specific to the safety and efficacy of the COVID-19 [4-7] 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 therapy, were available from observational studies in people who were 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.

There is one study that suggests that a third dose of COVID-19 vaccine in immunocompromised patients can increase antibody levels.[21] Small studies on third doses of the mRNA COVID-19 vaccines have shown that immunogenicity (immunity measured in the blood) may increase with a third dose. The safety of a third dose is unknown at this time for ARD, but in these small studies reactions were found to be similar to that of prior doses. The impact of additional doses on the worsening of underlying disease or on rare adverse events, including the risk of myocarditis and/or pericarditis, is unknown at this time.[13]

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.

When infected, 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 the patient's rheumatologist 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.[10,18,20] 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 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.[22] BCCDC has a list of the individual components and their purpose in the vaccines (www.bccdc.ca/health-info/diseases-conditions/covid-19/covid-19-vaccine/vaccines-for-covid-19). For a complete list of components in the vaccine, consult the vaccine monographs found at:

- tozinameran (COMIRNATY, Pfizer BioNTech): https://covid-vaccine.canada.ca/info/pdf/pfizer-biontech-covid-19-vaccine-pm1-en.pdf
- elasomeran (SPIKEVAX, Moderna): https://covid-vaccine.canada.ca/info/pdf/covid-19-vaccine-moderna-pm-en.pdf
- ChADOx1-S (VAXZEVRIA, AstraZeneca): https://covid-vaccine.canada.ca/info/pdf/astrazeneca-covid-19-vaccine-pm-en.pdf
- Ad26.COV2.S (Janssen COVID-19 Vaccine, Janssen): https://covid-vaccine.canada.ca/info/pdf/janssen-covid-19-vaccine-pm-en.pdf

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.

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.[23] 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[19] 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. Clinical advice to adjust Mycophenolate Mofetil around COVID-19 immunization (when the condition is stable) is derived from the American College of Rheumatology guidelines.[20]

For patients on the following medications, there is **no need to adjust or delay the medication**:

- **Adalimumab**
- **Anakinra**
- **Azathioprine**
- **Belimumab**
- **Canakinumab**
- **Certolizumab**
- **Cyclosporin**
- **Etanercept**
- **Golimumab**
- **Hydroxychloroquine**
- **Infliximab**
- **Intravenous immunoglobulin (IVIG)**
- **Ixekizumab**
- **Leflunomide**
- **Methotrexate**
- **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 likely more important to have the COVID-19 vaccine earlier than to delay based on timing of B-cell therapy.

For patients on **mycophenolate mofetil**, if the disease is stable, hold the medication for one week following a COVID-19 dose.[20]

*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 doses. Pediatric patients on high-dose steroids should consult with their pediatric rheumatologist to decide on the best time to receive the vaccine.[24]

NOTE: The American College of Rheumatology[20] differs from the Canadian Rheumatology Association with adjustment recommendations for the medications as follows. The authors of this guidance document are aligned with the Canadian Rheumatology Association's recommendations, with the exception of mycophenolate mofetil as described above. However, the American College's recommendations are available here and provided below for reference:

- *For patients on weekly **methotrexate (MTX)**, an option is to skip the MTX dose the following week after each vaccine dose.*
- *For patients on **tofacitinib**, **baricitinib, upadacitinib**, an option is to skip the medication for one week following each vaccine dose.*
- *For patients on **abatacept** weekly injections, an option is to skip the abatacept one week before and one 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 four weeks post-dose and postpone next infusion by one 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 one week prior to the next cyclophosphamide infusion.*

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