Canadian Rheumatology Association recommendation for the use of COVID-19 vaccination for patients with autoimmune rheumatic diseases

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ABSTRACT

Objective: To develop guidance on the use of COVID-19 vaccines in patients with autoimmune rheumatic diseases (ARD).

Methods: The Canadian Rheumatology Association (CRA) formed a multidisciplinary panel including rheumatologists, researchers, methodologists, vaccine experts and patients. The panel used the GRADE approach. Outcomes were prioritized according to their importance for patients and clinicians. Evidence from the COVID-19 clinical trials was summarized. Indirect evidence for non-COVID-19 vaccines in ARD was also considered. The GRADE Evidence-to-Decision (EtD) framework was used to develop a recommendation for the use of the four COVID vaccines approved in Canada as of March 25, 2021 (BNT162b2, mRNA-1273, ChAdOx1 and Ad26.COV2.S) over four virtual panel meetings.

Results: The CRA guideline panel suggests using COVID-19 vaccination in persons with ARD. The panel unanimously agreed that for the majority of patients the potential health benefits of vaccination outweigh the potential harms in people with ARDs. The recommendation was graded as conditional because of low or very low certainty of the evidence about the effects in the population of interest primarily due to indirectness and imprecise effect estimates. The panel felt strongly that persons with autoimmune rheumatic diseases who meet local eligibility should not be required to take additional steps compared to people without autoimmune rheumatic diseases to obtain their vaccination. Guidance on medications, implementation, monitoring of vaccine uptake and research priorities are also provided.

Conclusion: This recommendation will be updated over time as new evidence emerges, with the latest recommendation, evidence summaries and EtD available on the CRA website.

INTRODUCTION

Autoimmune rheumatic diseases (ARDs) include a range of chronic inflammatory conditions of the musculoskeletal and connective tissue systems, such as rheumatoid arthritis, systemic lupus erythematosus, and vasculitis. Vaccines are an important part of the care of people living with ARDs (1, 2). Owing to their disease, comorbidities associated with ARDs and/or medications, people with ARDs may be at higher risk for infections, or for developing worse outcomes from vaccine-preventable illnesses (3-6). While live vaccines are not recommended for patients taking certain immune suppressing medications, owing to a potential risk of infection, inactivated vaccines may be safely administered, although their effectiveness may be diminished by these medications (1, 2).

Recently approved COVID-19 vaccines have brought tremendous promise to help end a pandemic that has caused an unprecedented impact on people and society. As of March 2021, four vaccines were approved for use in Canada, with more on the horizon. These include mRNA vaccines BNT162b2 (Pfizer) (7) and mRNA-1273 (ModernaTX) (8) and viral vector vaccines ChAdOx1 (AstraZeneca) (9) and Ad26.COV2.S (Johnson & Johnson) (10). Through encapsulated lipid particles, mRNA vaccines deliver mRNA sequences for the spike protein of the SARS-CoV-2 virus. These mRNA sequences are translated into spike proteins in the recipient, that elicit an immune response (7, 8). Viral vector vaccines work similarly, but provide the genetic sequences for the spike protein on DNA, delivered through an attenuated adenovirus viral vector.

The clinical trials of the approved COVID vaccines conducted to date largely excluded patients with autoimmune conditions and/or people taking immune suppressing medications (7, 8). Given the lack of direct evidence, recommendations on the vaccine in people with ARDs have varied. In Canada, the National Advisory Committee on Immunization (NACI) initially made a strong recommendation against the vaccine in people with autoimmune conditions owing to the lack of direct evidence, but this has since been modified to indicate that the vaccine may be offered if the benefits outweigh the risk for the individual patient (11). Other rheumatology groups, including the American College of Rheumatology, British Society of Rheumatology, and a Position Statement from the Canadian Rheumatology Association (CRA), have more actively encouraged vaccination for this population (12-14).

Objective and need

The objective of these recommendations is to provide guidance for the use of COVID-19 vaccines in patients with ARDs. The guideline was approved by the Guidelines Committee of the CRA on January 15, 2021. The guideline was also deemed an urgent priority of the Canadian Arthritis Patient Alliance (CAPA).

Target audience

The target audience are patients with ARDs, physicians and other allied health professionals counselling patients regarding the COVID-19 vaccine.

Target population

This guideline is intended for individuals aged 16 years and older with ARDs. ARDs are a diverse group of autoimmune conditions that commonly affect the joints and other organs or systems. This includes, but is not limited to, conditions such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, myositis, polymyalgia rheumatica, Sjogren's syndrome and vasculitis (see Supplementary Text for additional, but not exhaustive list of conditions) (15). People with ARDs typically require long-term treatment with immune-modulating medications. ARDs do not include non-autoimmune conditions that can also affect joints or soft tissues such as osteoarthritis or fibromyalgia.

This guideline is intended for people with ARDs regardless of whether they are on current immune-modulating treatment or not. Treatments commonly used for these conditions include (1):

- Glucocorticoids
- Synthetic disease-modifying antirheumatic drugs (DMARDs): methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine
- Mycophenolic acid preparations
- Calcineurin inhibitors: cyclosporine, tacrolimus
- Alkylating agent: cyclophosphamide
- Biologic DMARDs (originator or biosimilars): infliximab, etanercept, adalimumab, certolizumab, golimumab, abatacept, tocilizumab, sarilumab, rituximab, secukinumab, ixekizumab, belimumab, anakinra, canakinumab
- Targeted synthetic DMARDs: tofacitinib, baricitinib, upadacitinib

Perspective

This guideline takes the perspective of the individual person living with an ARD. It does not consider population/health system issues related to vaccine prioritization or distribution.

MATERIALS AND METHODS

The CRA panel developed an initial recommendation for the approved mRNA vaccines between January 15-February 13, 2021 and updated this to include the approved viral vector vaccines on March 25, 2021. This guideline was developed using the GRADE approach, which provides a systematic process for appraising the certainty of evidence and grading the direction and strength of recommendations (16). Ethics approval was not required.

Organization and panel composition

The CRA assembled a guideline panel and included rheumatologists, methodologists, infectious disease physicians with expertise in vaccines, and two people living with ARDs (see Appendix A). The panel included expertise in health equity, patient preferences, vaccination in patients with ARDs, vaccine hesitancy, lived experience with ARDs, evidence synthesis and guideline development. Methodological support was provided by the Cochrane Musculoskeletal Centre for evidence synthesis and the McMaster GRADE Centre for guideline development. All panel meetings were held virtually by video calls. Seven panelists who did not have prior GRADE exposure or training completed a guideline development training course (International Guideline Development Credentialing & Certification Program; inguide.org) with focus on

GRADE prior to the start of the guideline development process, which was offered free of charge.

Guideline funding and management of conflicts of interest

The guideline was supported by in-kind funding from the CRA, a non-profit association that represents Canadian rheumatologists. The CRA also provides ongoing funding to the Cochrane Musculoskeletal Centre. Declarations of potential conflicts of interest (COI) were collected from all panelists and review team members (Supplementary Table 1) using the International Committee of Medical Journal Editors (ICMJE) form. The chair and co-chair, evidence review team and all members of the voting panel were required to be free of any direct financial COI within the past 36 months, which meant no direct payments including research funding support from any manufacturers of COVID-19 vaccines that were currently approved or in development as of the date of the panel meetings (17). Expert panel members with COI were allowed to participate in the discussion but did not vote on any of the judgements (Quality of Evidence, Evidence to Decision criteria, direction and strength of recommendation). The presence of direct financial COI was adjudicated by a staff member of the CRA separate from the guideline panel and discussed with the chair and co-chair in the setting of ambiguity. The full list of submitted COIs are presented online (https://rheum.ca/resources/cra-grade-recommendation-on-covid-19-vaccination-and-feedback-survey/).

Formulating clinical questions and determining outcomes of interest

The scope of the guideline was determined by the CRA to focus on whether COVID-19 vaccines should be used in persons with ARDs. No other questions were considered. Prior to the first meeting, a survey was circulated to the panel to agree on the definitions and specifications for population, interventions, and to rate the importance of the outcomes. In this initial guideline, the interventions were limited to approved COVID-19 vaccines as of March 25, 2021, but additional vaccines will be considered over time as they are approved for use in Canada.

Evidence review and grading of certainty of evidence

In order to identify the relevant data on COVID-19 vaccines, we used the resources available in covid-nma.com (18, 19), a living evidence synthesis of all randomized controlled trials of COVID-19 vaccines. We supplemented our evidence review with indirect evidence of the efficacy and safety of other vaccines in people with ARDs (see Supplementary Text 1 for full details). The certainty of the evidence for each outcome was categorized as very low, low, moderate or high, according to GRADE methodology (16). Randomized controlled trials started as high quality and judgements were made whether to rate the certainty downward for the 5 GRADE domains: risk of bias, inconsistency, indirectness, publication bias and imprecision (20). Observational evidence started as low quality and could be rated downward for the same 5 domains or could be rated upwards for 3 additional domains: presence of large effects, dose-response relationship, and the effect of plausible residual confounding (20).

Development of Recommendation

A recommendation for the 2 mRNA vaccines (BNT 162b2 and mRNA-1273) was first developed over 3 virtual panel meetings and published online. Subsequently, a recommendation for the Ad26.COV2.S and ChAdOx1 vaccines was developed during an additional panel meeting and the guideline was updated. GRADE Evidence-to-Decision (EtD) profiles were developed in GRADEpro software (https://gradepro.org). The EtDs included the summary of the evidence for desirable and undesirable effects with overall certainty of the evidence rating, and additional EtD domains of patient preferences and values, resource utilization, equity, acceptability and feasibility (21). Differences between the vaccines were highlighted. The EtDs were prepared by a central team (GH, JP, CB, RN) and reviewed by panel members prior to meetings. During the panel meetings, the panel discussed each EtD domain and then voted privately to the panel co-chair for each required judgement. The panel discussed the votes, and reached a consensus judgement, which required a simple majority (>50%) of the votes if there was disagreement. Following the EtD judgements, they then voted on the direction and strength of the recommendation. A simple majority (>50%) was required to determine the direction of the recommendation, and development of a strong recommendation required >=80% of the panel to agree.

How to read this guideline

In the GRADE approach, recommendations are categorized as strong or conditional (22). A strong recommendation means that all or almost all persons would choose that intervention. A conditional recommendation means that the majority of individuals in this situation would want the suggested course of action, but many would not (Table 1).

Living guideline

This guideline will be updated in a "living" fashion over time. Modifications will be planned when new vaccines are approved in Canada, or when new or higher certainty evidence (e.g. on an outcome in the population of interest), emerges. To identify new evidence, we will leverage an existing effort to identify and map national and international vaccine recommendations (23), a living evidence reviews of COVID-19 vaccine clinical trials (18, 19), and a Cochrane review of COVID-19 vaccine safety and efficacy in patients with ARDs (24).

Public commenting

The draft guideline was published for public commenting on the CRA website on January 15, 2021 at https://rheum.ca/resources/cra-grade-recommendation-on-covid-19-vaccination-and-feedback-survey/. The public comments will be reviewed on an ongoing basis and considered in future updates.

How to use this guideline

This recommendation is intended to help clinicians and patients make decisions regarding COVID-19 vaccination. It is not meant to replace clinical judgement. The recommendation should always be presented with the accompanying remarks to aid in interpretation. Guideline users should be aware that the recommendation is subject to change over time in a living fashion as new evidence emerges and should always consult the CRA website

(https://rheum.ca/resources/cra-grade-recommendation-on-covid-19-vaccination-and-feedback-survey/) for the latest version.

RESULTS

Should COVID-19 vaccination vs no COVID-19 vaccination be used for persons with ARD?

Recommendation: The Canadian Rheumatology Association guideline panel suggests using COVID-19 vaccination in persons with autoimmune rheumatic disease (conditional recommendation; low certainty of the evidence about effects for BNT 162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna) and Ad26.COV2.S (Johnson & Johnson); very low certainty for ChAdOx1 (AstraZeneca)).

Remark:

- This recommendation is based on evidence for the approved COVID-19 vaccines BNT 162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), Ad26.COV2.S (Johnson & Johnson), and ChAdOx1 (AstraZeneca).
- The recommendation needs to be viewed in the context of any restrictions to vaccine use for the general public set by national or provincial bodies, that may change over time.

Primary justification:

- The panel was unanimous that for the majority of patients the potential benefits outweigh the potential harms in people with ARDs. The recommendation was graded as conditional because of uncertainty about the effects in the population of interest.

Primary implementation consideration for policy makers and providers:

- Persons with autoimmune rheumatic diseases who meet local eligibility criteria for COVID-19 vaccination should not be denied access to vaccination and should not be required to take additional steps compared to people without autoimmune rheumatic diseases to obtain their vaccination.

Summary of the evidence

Benefits

The benefits of the COVID-19 vaccine were considered large for preventing symptomatic COVID-19 (all vaccines) and severe or critical COVID-19 (BNT 162b2, mRNA-1273, Ad26.COV2.S) (Tables 2-4). The panel unanimously agreed that there was an overall large magnitude of benefits for all vaccines. Some people with ARDs may have less protection from the vaccine, based on the medications they are taking. From data of other (non-COVID) vaccines, methotrexate, mycophenolate mofetil, tofacitinib and prednisone (≥10 mg/day) have also been shown to attenuate vaccine-induced responses [2]. A single small study with abatacept and influenza vaccine also showed decreased immunogenicity [7]. Emerging data in COVID-19 vaccines, suggests serological responses may also be reduced in patients taking certain

medications (25, 26). However, given the large magnitude of benefit, it is likely that the benefits of the vaccine will still be large for most ARD patients. One potential exception is with patients on rituximab treatment, as notable decreases in immunogenicity have been seen post-influenza vaccine [2, 8-11] (see subgroup considerations below).

The panel also discussed how the benefits of COVID-19 vaccination in absolute terms will vary based on an individual's risk of acquiring COVID-19, which will depend on place of residence, community transmission of COVID-19, occupation, and social and family contacts. The benefits of preventing severe disease will also vary by a patient's individual risk factors for COVID-19. While data has not suggested ARDs are an independent risk factor for severe COVID-19 [12-16], many persons with ARD are older and have higher rates of comorbidities [17-19] which are associated with more severe disease from COVID-19. In people with ARDs, higher disease activity and certain medications (including prednisone (≥ 10 mg/day) have been associated with an increased risk of hospitalization and/or death in those with COVID-19 infection [20, 21]. Finally, ARDs are also more prevalent in populations at risk for inequities in COVID-19 infection rates and outcomes (e.g. Indigenous populations) [22].

Additional potential benefits of the vaccine include avoiding isolation requirements associated with contracting COVID-19 infection, protecting loved ones, improved herd immunity, and helping end the pandemic. It was noted though that even if people receive the vaccine, it would still be important to continue following public health recommendations and not to assume they are protected from COVID-19. While this guideline took the perspective of the individual

patient decision, additional societal benefits could include increased herd immunity, reduction of virus persistence and mutations, and reduction of infection.

Harms

The point estimate for serious adverse events was either of negligible magnitude (mRNA vaccines) or favoured the vaccine (Ad26.COV2.S and ChAdOx1) (Tables 2-4). The point estimate for auto-immune adverse events favoured the vaccine for the mRNA vaccines (Table 2) and was not well reported for the other vaccines (Tables 3 and 4). The increase in any adverse events seen with the mRNA and Ad26.COV2.S vaccines was judged to be of trivial magnitude, given they were largely expected injection site or systemic reactions to the vaccine. The decrease in any adverse events seen with the ChAdOx1 vaccine was judged to be of trivial magnitude but the adverse event data for the ChAdOx1 vaccine was difficult to interpret because of the mixed comparator (meningococcal vaccine or placebo). There was no evidence from studies in other vaccines that immunization results in a significant increase in disease activity (flares) in patients with ARDs, although the available data was limited and heterogeneous in terms of types of vaccines, flare definitions, and populations studied (see Supplementary Figure 1 and Supplementary Tables 2-4) [2, 23]. The panel also discussed (March 25, 2021) the recent reports of very rare reports of vaccine-induced thrombotic thrombocytopenia (VITT) identified with the ChAdOx1 vaccine (27-29) and, subsequently with the Ad26.COV2.S vaccine (30). The panel felt that guidance from national/provincial bodies regarding the use of vaccines in the setting of new safety data should be followed; safety issues identified in the general population would also apply to people with AIRDs.

Certainty of Evidence: The certainty of evidence for each outcome is presented in the Evidence Profiles (Tables 2-4). All outcomes were rated down one level for indirectness given that patients with autoimmune disease and people on immunosuppressants were largely excluded from COVID-19 vaccine clinical trials (7, 8). There was moderate quality evidence for benefits and low (mRNA, Ad26.COV2.S) or very low (ChAdOx1) quality evidence for harms, which resulted in assigning an overall low or very low quality of evidence, primarily due to additional concerns about imprecision.

Other EtD criteria and considerations: The panel judged that a recommendation for the vaccine would be expected to increase health equity, as ARDs and COVID-19 are more prevalent and can be more severe in populations at risk for inequities for whom COVID-19 vaccines are being prioritized (31-33). Vaccination may also increase health equity by ensuring people with ARDs are able to re-engage with society at a similar rate to people without ARDs, as the pandemic eases (i.e. not be 'left behind'). This may help lessen challenges that people with ARDs already face with work, family and social life. The panel also discussed that in Canada, some patients with ARDs have had difficulty accessing the COVID-19 vaccine, despite being eligible based on provincial vaccine priority groups. The Ad26.COV2.S vaccine was judged to further increase health equity, as the single dose will be easier to administer. The panel felt strongly that people with ARDs should be able to access the COVID-19 vaccine without any additional barriers. People should be informed about the lack of direct evidence, but should not be required to take additional steps to obtain their vaccination (for instance, requiring physician

documentation or a letter). Vaccine clinics should be accessible to persons with disabilities given the functional and mobility impairments of people living with ARD's. Creating additional requirements was judged to increase inequities.

Conclusion: The panel balanced the moderate certainty in the large vaccine benefits against the low/very low certainty of evidence for harm. Although the magnitude of the best estimate of harms was judged to be trivial, the uncertainty in the evidence led to a conditional recommendation.

Subgroup considerations/medications

People taking rituximab: Based on serological studies from other vaccines, rituximab is expected to decrease immunogenicity (2). Prior guidelines for other vaccines in patients with ARDs have recommended that immunization be deferred to ⩾ 4-5 months after the last dose and at least 4 weeks prior to the subsequent dose of rituximab (2).

People taking other DMARDs: Some other DMARDs may reduce protection from the vaccine. Given the large magnitude of benefit of the COVID-19 vaccines, it is likely that the benefits of the vaccine will still be large for most ARD patients. Continuing medications will often be the safest option to prevent disease flares until more evidence is available. This is in line with guidance from the British Society of Rheumatology (14). Recent guidance from the American College of Rheumatology recommended holding some medications (methotrexate, JAK

inhibitors, abatacept) around the time of COVID-19 vaccination, but the full guideline had not been published and the evidence supporting this was unclear (12). The CRA COVID-19 guideline panel did not feel that this guidance could be endorsed at this point but will review new evidence as it emerges. Any decision to hold medications should be discussed between a patient and their rheumatologist or healthcare team.

Pregnant and breastfeeding women: Additional considerations apply for pregnant and breastfeeding women, which should be discussed between a patient and their perinatal care team. These were not covered in the scope of this guideline.

Implementation considerations

As vaccine access is determined by provincial health authorities, it will be essential to ensure people with ARDs do not face unnecessary additional barriers to vaccine access. For instance, people with ARDs should not be required to obtain a physician letter as proof of an informed decision discussion. A decision tool, co-developed by the Canadian Rheumatology Association and the Canadian Arthritis Patient Alliance to support decision-making for the COVID-19 vaccine in people with ARDs is available at: https://rheum.ca/decision-aid/ (13). People with ARDs may also have mobility limitations and appropriate access to vaccine clinics should be ensured. Finally, the available data is for on-label dosing (doses separated by 1-month for mRNA and ChAdOx1 vaccines). Given that people with ARDs may have reduced vaccine-induced immunity, the benefits of off-label dosing may be lower compared to people without AIRDs. As such, the CRA has recently advocated for on-label dosing for immunosuppressed patients (13).

Monitoring and evaluation

Monitoring of vaccine uptake should occur in people with ARDs, including populations at risk of inequity. Low uptake may point to barriers to access or hesitancy. The frequency of serious adverse events, disease flares, and COVID-19 infection/serious outcomes should be followed in patients with ARDs who do and do not receive the vaccine. People with ARDs should be encouraged to track their immunization history using an online Canadian vaccination tracker, developed with funding support from the Public Health Agency of Canada (https://www.canimmunize.ca/en/home).

Research recommendations: The panel proposed several research priorities, summarized in Table 5.

DISCUSSION

In this paper we present the CRA's Recommendation for COVID-19 vaccination in people with ARDs. This recommendation will be updated in a living fashion over time as new evidence and new vaccines are approved.

A strength of our approach was using GRADE methodology. We present our full EtD Framework, which provides transparency to our process and outlines the rationale supporting our recommendation. We included appropriate stakeholders throughout the process, including rheumatologists, experts in vaccination, methodologists and people with lived experience of

ARDs. We identified research priorities along with a rationale how the research links to key aspects of our EtD process and how future evidence might impact the recommendation. Our evidence review include the pivotal trials of the COVID-19 vaccines, as well as other indirect evidence on vaccine safety and efficacy in patients with ARDs. Limitations of our approach include the use of secondary reviews, which may have resulted in missing some newer studies of other non-COVID vaccines, although this would not have changed our recommendation, as the data would still be indirect. We focused on currently approved vaccines, but others will be added as they are approved in Canada.

Our recommendation in support of COVID-19 vaccination aligns with those of other rheumatology groups. The British Society of Rheumatology recommended the use of the COVID-19 vaccine for immunosuppressed patients, although no evidence review or evidence to decision process was presented (14). The American College of Rheumatology developed COVID-19 vaccination guidance through a Delphi process and evidence review (12). The ACR recommended that patients should receive COVID-19 vaccination, also making a conditional recommendation. As the groups used different approaches, it is difficult to directly compare language. A conditional recommendation should not be interpreted as less supportive of vaccination, particularly in patients at higher risk of COVID-19 infection outcomes, which will include many patients with ARD. In these patients, the benefits of COVID-19 vaccination will clearly outweigh any theoretical risks. Our conditional recommendation reflects the lack of direct evidence and as such some patients at particularly low risk of severe COVID outcome might prefer to wait until additional direct evidence is available. We have developed an

information sheet to support decision making for patients with ARDs (13). This is freely available and can be modified and adapted on request to other populations.

Important differences are present between our approach and the approach from the National Advisory Committee on Immunization (NACI) in Canada, despite both using GRADE (11). Most notably, NACI cited an absence of evidence in patients with auto-immune conditions when making a recommendation initially against the vaccine. However, a lack of direct evidence should not be interpreted as a complete absence of evidence. GRADE provides guidance in this regard. In situations where the population of interest does not match the population studied in the clinical trials, reviewers need to decide whether to rate the certainty of evidence down for indirectness (34). This situation is not uncommon in clinical medicine. Indeed, in rheumatology practice, patients treated in practice often differ from those included in clinical trials (35, 36). GRADE states that "one should not rate down for population differences unless one has compelling reason to think that the biology in the population of interest is so different from that of the population tested that the magnitude of effect will differ substantially" (34). Researchers should also be cautious not to rate the quality of evidence down for indirectness without sufficient rationale, so not to increase inequities in vulnerable populations who are often excluded from clinical trials (37). Our panel decided to rate the certainty of evidence down one level for indirectness for all outcomes. The fact that these vaccines employed a new technology influenced this, but the safety of other vaccines in people with ARDs, and very low rates of auto-immune adverse events seen in the clinical trials of COVID-19 vaccines (with no differences between groups) tempered this.

One of the key considerations with the vaccine is in regards to health equity. The COVID-19 pandemic has disproportionately affected many vulnerable groups including people living with ARDs (38). This community has faced drug shortages, disruptions in accessing health care professionals, medication supply restrictions as well as increased anxiety and fear of what contracting COVID-19 will mean to them and their families (39, 40). The remarkable development of highly effective COVID-19 vaccines has provided hope to patients with ARDs. The panel felt very strongly and unanimously that all patients with ARDs should not have any additional barriers to vaccine access, such as requiring a physician's letter, which may be difficult for some vulnerable populations, especially given some difficulties in accessing healthcare practitioners. As our recommendation focused on the individual patient decision, rather than a population perspective, we did not consider issues of vaccine prioritization. We do note that other groups have recommended patients with ARDs are in a higher priority group (12), and this has recently been implemented in several provinces in Canada. We are certainly supportive of this decision and believe it will help lessen the impact on vulnerable communities.

In summary, we present the CRA's recommendation for the use of COVID-19 vaccines in patients with ARDs. We provide a recommendation for the use of COVID-19 vaccines, as well as subgroup considerations for patients taking certain medications. This recommendation will be updated over time, with the latest recommendation hosted on the CRA website.

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REFERENCES

1. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of eular recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79:39-52.
2. Papp KA, Haraoui B, Kumar D, Marshall JK, Bissonnette R, Bitton A, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. J Cutan Med Surg 2019;23:50-74.
3. Yun H, Yang S, Chen L, Xie F, Winthrop K, Baddley JW, et al. Risk of herpes zoster in autoimmune and inflammatory diseases: Implications for vaccination. Arthritis Rheumatol 2016;68:2328-37.
4. Shigayeva A, Rudnick W, Green K, Chen DK, Demczuk W, Gold WL, et al. Invasive pneumococcal disease among immunocompromised persons: Implications for vaccination programs. Clin Infect Dis 2016;62:139-47.
5. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. Arthritis Rheum 2002;46:2287-93.
6. Chang CC, Chang YS, Chen WS, Chen YH, Chen JH. Effects of annual influenza vaccination on morbidity and mortality in patients with systemic lupus erythematosus: A nationwide cohort study. Sci Rep 2016;6:37817.
7. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the bnt162b2 mrna covid-19 vaccine. N Engl J Med 2020;383:2603-15.
8. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mrna-1273 sars-cov-2 vaccine. N Engl J Med 2020.
9. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the chadox1 ncov-19 vaccine (azd1222) against sars-cov-2: An interim analysis of four randomised controlled trials in brazil, south africa, and the uk. Lancet 2021;397:99-111.
10. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose ad26.Cov2.S vaccine against covid-19. N Engl J Med 2021.
11. National Advisory Committee on Immunization (NACI). Recommendations on the use of covid-19 vaccines. December 23 2020 [updated December 23 2020; cited]; Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html.
12. ACR COVID-19 Vaccine Clinical Guidance Task Force. Covid-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases. 2021 [updated 2021; cited]; Available from: https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf.
13. Canadian Rheumatology Association. Canadian rheumatology association position statement on covid-19 vaccination. 2020 [updated 2020; cited]; Available from: https://mcusercontent.com/912adf891f7fdc4dfefb739ba/files/0df3fde1-a4a3-4f24-b6f5-eb4b3e053c11/CRA_Position_Statement_on_COVID_19_Vaccination_v2_FINAL.pdf.
14. British Society for Rheumatology. Covid-19 guidance. 2020 [updated 2020; cited]; Available from: https://www.rheumatology.org.uk/practice-quality/covid-19-guidance.

15. Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. Lancet 2013;382:797-808.
16. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. Grade guidelines: 1. Introduction-grade evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.
17. Craven J. Covid-19 vaccine tracker. 2021 [updated 2021; cited]; Available from: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker.
18. Boutron I, Chaimani A, Meerpohl JJ, Hrobjartsson A, Devane D, Rada G, et al. The covid-nma project: Building an evidence ecosystem for the covid-19 pandemic. Ann Intern Med 2020;173:1015-7.
19. Boutron I, Chaimani A, Devane D, Meerpohl JJ, Rada G, Hróbjartsson A, et al. Interventions for the prevention and treatment of covid-19: A living mapping of research and living network meta-analysis. Cochrane Database of Systematic Reviews 2020.
20. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. Grade guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.
21. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. Grade guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726-35.
22. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ 2008;336:1049-51.
23. Covid19 recommendations and gateway to contextualization. Journal [serial on the Internet]. Date: Available from: https://covid19.evidenceprime.ca/.
24. Whittle SL, Hazlewood GS, Robinson P, Johnston RV, Leder K, Glennon V, et al. Covid-19 vaccination for people with autoimmune rheumatic diseases on immunomodulatory therapies [protocol]. Cochrane Database of Systematic Reviews 2021;[in press].
25. Geisen UM, Berner DK, Tran F, Sumbul M, Vullriede L, Ciripoi M, et al. Immunogenicity and safety of anti-sars-cov-2 mrna vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. Ann Rheum Dis 2021.
26. Boyarsky BJ, Ruddy JA, Connolly CM, Ou MT, Werbel WA, Garonzik-Wang JM, et al. Antibody response to a single dose of sars-cov-2 mrna vaccine in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis 2021.
27. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after chadox1 ncov-19 vaccination. N Engl J Med 2021.
28. Schultz NH, Sorvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after chadox1 ncov-19 vaccination. N Engl J Med 2021.
29. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after chadox1 ncov-19 vaccination. N Engl J Med 2021.
30. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. Us case reports of cerebral venous sinus thrombosis with thrombocytopenia after ad26.Cov2.S vaccination, march 2 to april 21, 2021. JAMA 2021.
31. Government of Canada. Recommendations on the use of covid-19 vaccines. . Journal [serial on the Internet]. 2021 Date: Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html.

32. Hurd K, Barnabe C. Systematic review of rheumatic disease phenotypes and outcomes in the indigenous populations of canada, the USA, australia and new zealand. Rheumatol Int 2017;37:503-21.
33. Barnabe C. Disparities in rheumatoid arthritis care and health service solutions to equity. Rheum Dis Clin North Am 2020;46:685-92.
34. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. Grade guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011;64:1303-10.
35. Choi MY, Barnabe C, Barber CE, Bykerk V, Pope JE, Hazlewood GS. Pragmaticism of randomized controlled trials of biologic treatment with methotrexate in rheumatoid arthritis: A systematic review. Arthritis Care Res (Hoboken) 2019;71:620-8.
36. Monti S, Grosso V, Todoerti M, Caporali R. Randomized controlled trials and real-world data: Differences and similarities to untangle literature data. Rheumatology (Oxford) 2018;57:vii54-vii8.
37. Welch VA, Akl EA, Pottie K, Ansari MT, Briel M, Christensen R, et al. Grade equity guidelines 3: Considering health equity in grade guideline development: Rating the certainty of synthesized evidence. J Clin Epidemiol 2017;90:76-83.
38. Feldman CH, Ramsey-Goldman R. Widening disparities among patients with rheumatic diseases in the covid-19 era: An urgent call to action. Arthritis Rheumatol 2020;72:1409-11.
39. Mehta B, Jannat-Khah D, Fontana MA, Moezinia CJ, Mancuso CA, Bass AR, et al. Impact of covid-19 on vulnerable patients with rheumatic disease: Results of a worldwide survey. RMD Open 2020;6.
40. Michaud K, Wipfler K, Shaw Y, Simon TA, Cornish A, England BR, et al. Experiences of patients with rheumatic diseases in the united states during early days of the covid-19 pandemic. ACR Open Rheumatol 2020;2:335-43.

1 Table 1. Interpretation of Strong and Conditional Recommendations

Implications for:	**Strong recommendation**	**Conditional recommendation**
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Table 2. Summary of Findings Table for BNT 162b2 and mRNA-1273 (mRNA) COVID-19 Vaccines in People with Autoimmune Rheumatic Disease (interactive table available online)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with COVID vaccine			
Mortality	30 per 100,000	**22 per 100,000** (9 to 54)	**RR 0.73** (0.29 to 1.81)	73603 (2 RCTs)	⨁⨁◯◯ LOW [a,b]
Severe or critical disease	110 per 100,000	**4 per 100,000** (1 to 21)	**RR 0.04** (0.01 to 0.19)	70780 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]
Incidence of symptomatic COVID-19 confirmed with positive test	1,099 per 100,000	**55 per 100,000** (33 to 99)	**RR 0.05** (0.03 to 0.09)	63129 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]
Severe Adverse Events	717 per 100,000	**739 per 100,000** (624 to 875)	**RR 1.03** (0.87 to 1.22)	73603 (2 RCTs)	⨁⨁◯◯ LOW [a,b]
Autoimmune adverse events	13 per 100,000	**7 per 100,000** (1 to 73)	**RR 0.50** (0.05 to 5.51)	30351 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]
Incidence of any adverse events	16,075 per 100,000	**25559 per 100,000** (24,755 to 26,362)	**RR 1.59** (1.54 to 1.64)	73603 (2 RCTs)	⨁⨁◯◯ LOW [a,c]
Exacerbation of pre-existing disease	Immunization did not generally cause clinically significant worsening of underlying ARDs. A meta-analysis evaluating the impact of influenza and pneumococcal vaccination in systemic lupus erythematosus (SLE) demonstrated that immunization had no significant effect on the SLE disease activity index (SLEDAI) score.			759 (20 observational studies)	⨁◯◯◯ VERY LOW [d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

a. Downgraded one level for indirectness due to the population of interest being excluded from the trials

b. Downgraded one level for imprecision due to confidence interval including serious benefits and serious harms

c. Downgraded one level for inconsistency due to extreme heterogeneity $Chi^2 = 513.92$, df = 1 ($P < 0.00001$); $I^2 = 100\%$

d. Downgraded one level for indirectness due to vaccine of interest not included in the studies

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 3. Summary of Findings Table for Ad26.COV2.S COVID-19 Vaccine in People with Autoimmune Rheumatic Disease (interactive table available online)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with Ad26.COV2.S COVID vaccine			
Mortality	91 per 100,000	**69 fewer per 100,000** (83 fewer to 30 fewer)	**RR 0.25** (0.09 to 0.67)	43783 (1 RCT)	⨁⨁◯◯ LOW [a,b]
Severe or critical disease	409 per 100,000	**311 fewer per 100,000** (352 fewer to 250 fewer)	**RR 0.24** (0.14 to 0.39)	39058 (1 RCT)	⨁⨁⨁◯ MODERATE [a]
Incidence of symptomatic COVID-19 confirmed with positive test	1,796 per 100,000	**1,203 fewer per 100,000** (1,311 fewer to 1,060 fewer)	**RR 0.33** (0.27 to 0.41)	39058 (1 RCT)	⨁⨁⨁◯ MODERATE [a]
Severe Adverse Events	439 per 100,000	**61 fewer per 100,000** (158 fewer to 70 more)	**RR 0.86** (0.64 to 1.16)	43783 (1 RCT)	⨁⨁◯◯ LOW [a,c]
Autoimmune adverse events	"There were single reports of Guillain-Barre Syndrome (GBS) in a 60-year-old vaccine recipient and a 75-year-old placebo recipient occurring on Days 16 and 10, respectively. The event in the vaccine group was preceded by symptoms of chills, nausea, diarrhea and myalgia. In FDA's assessment the events of [...] GBS are unlikely related to study vaccine but a causal relationship cannot be definitively excluded."			(0 RCTs)	⨁◯◯◯ VERY LOW [a,d]
Incidence of any adverse events	19,438 per 100,000	**30,712 more per 100,000** (27,019 more to 34,794 more)	**RR 2.58** (2.39 to 2.79)	6736 (1 RCT)	⨁⨁⨁◯ MODERATE [a]
Exacerbation of pre-existing disease	Immunization did not generally cause clinically significant worsening of underlying ARDs. A meta-analysis evaluating the impact of influenza and pneumococcal vaccination in systemic lupus erythematosus (SLE) demonstrated that immunization had no significant effect on the SLE disease activity index (SLEDAI) score.			759 (20 observational studies)	⨁◯◯◯ VERY LOW [d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio
a. Downgraded one level for indirectness as auto-immune patients were not included in the trials
b. Downgraded one level for imprecision due to small number of events
c. Downgraded one level for imprecision due to confidence interval including serious benefits and serious harms
d. Imprecision downgraded by 2 levels due to scarcity of data and insufficient reporting.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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Table 4. Summary of Findings Table for ChAdOx1 COVID-19 Vaccine in People with Autoimmune Rheumatic Disease (interactive table available online)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with MenACWY/ placebo	Risk with ChAdOx1 SD/SD COVID vaccine			
Mortality	33 per 100,000	**17 fewer per 100,000** (30 fewer to 56 more)	**RR 0.49** (0.09 to 2.66)	24244 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]
Severe or critical disease	9 per 100,000	**6 fewer per 100,000** (8 fewer to 60 more)	**RR 0.33** (0.01 to 7.98)	23745 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]
Incidence of symptomatic COVID-19 confirmed with positive test	2,890 per 100,000	**1,937 fewer per 100,000** (2,226 fewer to 1,648 fewer)	**RR 0.33** (0.23 to 0.43)	17177 (1 RCT)	⨁⨁⨁◯ MODERATE [a]
Severe Adverse Events	1,062 per 100,000	**180 fewer per 100,000** (382 fewer to 74 more)	**RR 0.83** (0.64 to 1.07)	24244 (1 RCT)	⨁◯◯◯ VERY LOW [c,d]
Autoimmune adverse events	There were three cases of transverse myelitis (two in the vaccine group, one in the placebo). It is not clear enough in the reporting if there were other potentially autoimmune adverse events.			(0 RCTs)	⨁◯◯◯ VERY LOW [c,e]
Incidence of any adverse events	1,053 per 100,000	**274 fewer per 100,000** (463 fewer to 42 fewer)	**RR 0.74** (0.56 to 0.96)	23983 (1 RCT)	⨁⨁◯◯ LOW [c]
Exacerbation of pre-existing disease	Immunization did not generally cause clinically significant worsening of underlying ARDs. A meta-analysis evaluating the impact of influenza and pneumococcal vaccination in systemic lupus erythematosus (SLE) demonstrated that immunization had no significant effect on the SLE disease activity index (SLEDAI) score.			759 (20 observational studies)	⨁◯◯◯ VERY LOW [d]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

a. Downgraded one level because autoimmune patients were excluded from the trials.
b. Imprecision downgraded by 2 levels due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and few events.
c. Downgraded two levels for indirectness because autoimmune patients were excluded from the trials and the control groups mixed a placebo and an active component (meningitis vaccine).
d. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for no effect and the possibility for benefit.
e. Imprecision downgraded by 2 levels due to scarcity of data and insufficient reporting.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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Table 5: Research priorities related to COVID-19 vaccines in people with autoimmune rheumatic diseases

Research priority	**Rationale**
Observational evidence on the frequency of harms (in particular serious adverse events/serious disease flares) in people with ARDs	If very infrequent, may lower the importance of these outcomes
Evidence comparing the frequency of serious adverse events and autoimmune adverse events in people with ARDs to those without ARDs	If not different with sufficient certainty, the panel may decide not to rate the quality of evidence for harms down for indirectness
Evidence on the benefits (both clinical outcomes and serological studies) in people with ARDs on different medications, including the impact of off-label dosing on effectiveness	May help inform decisions regarding whether to hold medications around the time of vaccination and recommendations on optimal dosing intervals for 2-dose vaccines
Evidence on patient values preferences for the benefits and harms across different patient populations	Will help inform the relative importance of the outcomes
Understanding vaccine hesitancy and barriers to vaccine access faced by persons with ARDs	Will help inform strategies to address vaccine hesitancy
Understanding vaccine benefits and harms in populations at risk for inequities.	Will help inform strategies to address inequity in vaccine access and uptake