AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Empowering rheumatology professionals to excel in their specialty

2200 Lake Boulevard NE, Atlanta, GA 30319
Phone: (404) 633-3777 • Fax (404) 633-1870 • www.rheumatology.org

COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases

Version 5

Revised February 2, 2022

Developed by the ACR COVID-19 Vaccine Clinical Guidance Task Force

*This summary was initially approved by the ACR Board of Directors on February 8, 2021 and updated on March 4, 2021. A full paper (Version 1), was published in Arthritis & Rheumatology on May 24, 2021.**

*New recommendations regarding mycophenolate, methotrexate, acetaminophen, and NSAID timing considerations+ were added to this summary on April 28, 2021 and were added to the full paper (Version 2), which was published in Arthritis & Rheumatology on June 15, 2021.***

*Updated recommendations regarding age restrictions, preferences between specific vaccines, and need for continued preventive measures were added to this summary on June 19, 2021 and were added to the full paper (Version 3), which was published in Arthritis & Rheumatology on August 4, 2021.****

Updated recommendations regarding preference for use of mRNA vaccines, use of a supplemental vaccine dose (i.e., 'booster') and associated temporary interruption of immunomodulatory medications, and the FDA EUA for post-exposure prophylaxis with monoclonal antibody treatment for vaccinated AIIRD patients were added to this summary on August 19, 2021. These recommendations were added to the full paper (Version 4), which will be submitted to Arthritis & Rheumatology for publication.

Updated recommendations for supplemental (booster) dosing and revised information for holding immunomodulatory medications were added to the version 4 summary on October 27, 2021 and December 15, 2021. These recommendations were added to the full paper (Version 4), which will be submitted to Arthritis & Rheumatology for publication.

Updated recommendations differentiating supplemental and booster doses, including timing considerations, were added to the version 5 summary on January 28, 2022 and February 2, 2022. Revised guidance is also provided related to pre- and post-exposure prophylaxis with monoclonal antibody treatment, considering updated EUAs. These recommendations were added to the full paper (Version 5), which will be submitted to Arthritis & Rheumatology for publication.

Purpose

The purpose of this document is to provide guidance to rheumatology providers on the use of the COVID-19 vaccine and the associated management of rheumatic and musculoskeletal disease patients around the time of vaccination against SARS-CoV-2. These statements were based upon a dearth of high-quality data and are not intended to replace clinical judgment. Modifications made to treatment plans, particularly in complex rheumatic disease patients, are highly disease-, patient-, geography-, and time-specific and, therefore, must be individualized as part of a shared decision-making process. This guidance is provided as part of a 'living document,' recognizing rapidly evolving evidence and the anticipated need for frequent updates as such evidence becomes available. The target audience for this guidance is providers and patients in the United States, although the ACR recognizes that people outside of the U.S. may read and use the information provided here.

The target audience for this guidance is providers and patients in the United States, although the ACR recognizes that people outside of the U.S. may read and use the information provided here.

Methods

The North American Task Force panel, consisting of 9 rheumatologists, 2 infectious disease specialists, and 2 public health experts with current or past employment at the Centers for Disease Control (CDC), convened multiple times in December 2020 and January 2021. The Task Force proposed a variety of clinical questions related to COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases (RMD), divided itself into subgroups (i.e., teams), and assigned the clinical

questions to the various teams by topic (e.g., vaccine effectiveness, safety). Each team was charged to generate an evidence review covering that topic; the evidence reviews were combined into an evidence summary document that was collated and disseminated to the entire Task Force. The Task Force reviewed the clinical questions and associated proposed vaccine guidance statements that were evaluated using a well-established method of consensus building (modified Delphi process). This process included two rounds of asynchronous anonymous rating by email and two live webinars including the entire Task Force. Panel members rated their agreement with draft statements using a numeric scoring system, and consensus was determined to be either "moderate" (M) or "high" (H), based on the dispersion in the rating results. To be approved as guidance, median ratings were required to correlate to pre-defined levels of agreement (with median values interpreted as "agreement," "uncertainty" or "disagreement") with either moderate or high levels of consensus based on the statements as they were originally voted upon, unless they were subsequently reconsidered. For this summary document, several rating statements that were initially separate were combined to facilitate clarity and conciseness.

Results and Conclusion

General considerations related to COVID-19 vaccination in rheumatic and musculoskeletal disease patients are shown in Table 1. Statements more specific to patient groups, as well as general disease- and timing-related considerations, are presented in Table 2. No evidence was found to support a concern regarding the use or timing of immunomodulatory therapies in relation to vaccine safety. Therefore, guidance regarding immunomodulatory medication and vaccination timing (Table 3) was given considering the intent to optimize vaccine response. An important set of guiding principles, foundational assumptions and limitations are mentioned in the Supplemental Table. The ACR is committed to updating this guidance as a 'living document' as new evidence emerges. Statements in **bold** are those that have been revised or added in the most current version of the document. These changes are summarized in Appendix Table 2.

Recommendations

Table 1: General Considerations Related to COVID-19 Vaccination in Rheumatic and Musculoskeletal Disease Patients

	Guidance Statement	Level of Task Force consensus
	The rheumatology healthcare provider is responsible for engaging the RMD patient in a discussion to assess COVID-19 vaccination status and engage in a shared decision-making process to discuss receiving the COVID-19 vaccine.	Strong-Moderate
	Acknowledging heterogeneity due to disease- and treatment-related factors, and after considering the influence of age and sex, AIIRD patients are at higher risk for hospitalized COVID-19 and worse outcomes compared to the general population.	Moderate
	Based on their risk for COVID-19, AIIRD patients should be prioritized for vaccination before the non-prioritized general population of similar age and sex.	Moderate
	Beyond known allergies to vaccine components, there are no known additional contraindications to COVID-19 vaccination for AIIRD patients.	Moderate
	The expected response to COVID-19 vaccination for many AIIRD patients on systemic immunomodulatory therapies is blunted in its magnitude and duration compared to the general population.	Moderate
	A theoretical risk exists for AIIRD flare or disease worsening following COVID-19 vaccination. However, the benefit of COVID-19 vaccination for RMD patients outweighs the potential risk for new onset autoimmunity.	Moderate

RMD = rheumatic and musculoskeletal disease; AIIRD=autoimmune and inflammatory rheumatic disease

Table 2: Recommendations for Primary and Supplemental Dosing of the COVID-19 Vaccine in RMD Patients*

Guidance Statement	Level of Task Force consensus
RMD and AIIRD patients should receive COVID-19 vaccination, consistent with the age restriction of the EUA and/or FDA approval.†	Moderate
RMD patients without an AIIRD who are on immunomodulatory therapy should be vaccinated in a similar fashion as described in this guidance for AIIRD patients receiving those same treatments.	Moderate
For AIIRD patients not yet vaccinated, either of the mRNA vaccines is recommended over the J&J vaccine. There is no recommendation for one mRNA vaccine over another.	Moderate
For a multi-dose vaccine, AIIRD patients should receive the second dose of the same vaccine, even if there are non-serious adverse events associated with receipt of the first dose, consistent with timing described in CDC guidelines.	Strong
AIIRD patients who completed the primary COVID vaccine series and are expected to have mounted an inadequate vaccine response should receive a supplemental dose (e.g., a 3rd dose) as recommended by the CDC for immunocompromised individuals	Strong
For patients who previously completed the mRNA COVID-19 vaccine series or 1-dose J&J COVID-19 vaccine, and who are receiving a supplemental dose, an mRNA vaccine dose of either type (Pfizer or Moderna) is preferred.	Moderate
RMD patients who have completed a primary COVID vaccine series, and any supplemental doses for which they qualify, should receive booster dose(s) as recommended by the CDC for immunocompromised individuals. †	**Strong**
Primary vaccination, supplemental dosing, and booster doses should be given regardless of whether patients have experienced natural COVID-19 infection.	**Strong**
Healthcare providers should not routinely order any lab testing (e.g., antibody tests for IgM and/or IgG to spike or nucleocapsid proteins) to assess immunity to COVID-19 post-vaccination, nor to assess the need for vaccination in a yet-unvaccinated person.‡	Strong
Following COVID-19 vaccination, RMD patients should continue to follow all public health guidelines regarding physical distancing and other preventive measures.§	Strong
For high-risk AIIRD patients, pre-exposure prophylaxis monoclonal antibody treatment is recommended when available, if licensed or approved under FDA EUA**	Moderate
AIIRD patients at high risk for poor outcomes related to COVID should receive monoclonal antibody therapy, either as prevention (i.e., post-exposure prophylaxis for asymptomatic, recently exposed patients) or as treatment for newly symptomatic patients, if licensed or approved under FDA EUA**	Moderate
Household members and other frequent, close contacts of AIIRD patients should undergo COVID-19 vaccination when available to them to facilitate a 'cocooning effect' that may help protect the AIIRD patient. No priority for early vaccination is recommended for household members.	Moderate
While vaccination would ideally occur in the setting of well-controlled AIIRD, except for those patients with life-threatening illness (e.g., in the ICU for any reason), COVID vaccination should occur as soon as possible for those for whom it is being recommended, irrespective of disease activity and severity.	Strong-Moderate

* RMD = rheumatic and musculoskeletal disease; AIIRD=autoimmune and inflammatory rheumatic disease; EUA = Emergency Use Authorization; FDA = US Food and Drug Administration; mRNA = messenger RNA; CDC = Centers for Disease Control and Prevention; ICU = intensive care unit

† Age ≥5 as of October 29, 2021

† The timing of booster shot intervals is vaccine dependent. For both the Moderna and Pfizer mRNA vaccines, a booster shot is recommended at least 5 months after completion of the primary vaccine series. The recommended interval for those having received the J&J vaccine is at least 2 months. (See https://www.cdc.gov/media/releases/2022/s0104-Pfizer-Booster.html and https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-shortens-interval-booster-dose-moderna-covid-19-vaccine-five-months)

‡ Given uncertainties in the interpretation of lab testing following vaccination as it would impact clinical decision-making, the panel reaffirmed this statement in Version 4 of this guidance document.

§ The Task Force discussed the possibility of recommending additional and more sustained public health measures in AIIRD patients. After deliberation, they did not elect to exceed current public health authority guidance given uncertainties about the clinical effectiveness of vaccination in such patients. The appropriateness for continued preventive measures (e.g., masking, physical distancing) should be discussed with patients as their rheumatology providers deem appropriate.

** High risk is defined as moderate to severely compromised immune systems who may not mount an adequate immune response to COVID-19 vaccination. **Note that FDA authorization and CDC recommendations will be influenced based upon the dominant variants of SARS-CoV-2 circulating in the U.S. (see https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron; and https://emergency.cdc.gov/han/2021/han00461.asp).**
At the time of this update, neither bamlanivimab and etesevimab (administered together) nor casirivimab and imdevimab, are licensed or available under FDA EUA given their lack of activity against the Omicron variant, the dominant strain circulating in the U.S. See Appendix Table 1 for further details.

Table 3: Guidance Related to the Use and Timing of Vaccine Dosing and Immunomodulatory Therapy in Relation to COVID-19 Vaccination in RMD Patients*

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination (applies to both primary vaccination and supplemental [booster] dosing)	Level of Task Force Consensus
Abatacept IV	Time vaccination so that it occurs one week prior to the next dose of IV abatacept	Moderate
Abatacept SQ	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate
Acetaminophen, NSAIDs	Assuming that disease is stable, hold for 24 hours prior to vaccination. No restrictions on use post vaccination once symptoms develop.	Moderate
Belimumab SQ	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate
TNFi, IL-6R, IL-1R, IL-17, IL12/23, IL-23, and other cytokine inhibitors†	The Task Force failed to reach consensus on whether or not to temporarily interrupt these following each COVID vaccine dose, including both primary vaccination and supplemental (booster) dosing	Moderate
Cyclophosphamide IV	Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible	Moderate
Hydroxychloroquine, **IVIG**	**No modifications to either immunomodulatory therapy or vaccination timing**	Strong (HCQ), **Moderate (IVIG)**
Rituximab or other anti-CD20 B-cell depleting agents	Discuss the optimal timing of dosing and vaccination with the rheumatology provider before proceeding‡	Moderate
All other conventional and targeted immunomodulatory or immunosuppressive medications (e.g., JAKi, MMF) except those listed above§	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate

Note: individual medications that were specifically voted on by the task force are listed on separate rows and were not collapsed, even if the resulting recommendation was similar to others.

***** RMD = rheumatic and musculoskeletal disease; IVIG = intravenous immunoglobulin; TNFi = tumor necrosis factor inhibitor; IL = interleukin; JAKi = janus kinase inhibitor; CYC = cyclophosphamide; RTX = rituximab; IV = intravenous; SQ = subcutaneous; NSAID = non-steroidal anti-inflammatory drugs; MMF = mycophenolate mofetil; ***JAKi = baricitinib, tofacitinib, upadacitinib***

† Examples of specific cytokine inhibitors are as follows: IL-6R = sarilumab; tocilizumab; IL-1R = anakinra, canakinumab; IL-17 = ixekizumab, secukinumab; IL-12/23 = ustekinumab; IL-23 = guselkumab, rizankizumab

‡ *Some practitioners measure CD19 B cells as a tool with which to time the booster and subsequent rituximab dosing. For those who elect to dose without such information, or for whom such measurement is not available or feasible, provide a supplemental dose 2-4 weeks before next anticipated rituximab dose (e.g., at month 5.0 or 5.5 for patients on an every 6 month rituximab dosing schedule)*

§ Includes apremilast; azathioprine; calcineurin inhibitors; cyclophosphamide (oral); IVIG; leflunomide; methotrexate, janus kinase inhibitors [JAKi] (baricitinib, tofacitinib, upadacitinib), mycophenolate; sulfasalazine

Supplemental Table: Foundational Principles, Assumptions, and Considerations for the Guidance Statements

ACR guidance statements are not intended to supersede the judgement of rheumatology care providers nor override the values and perspectives of their patients. Guidance was based on weak and/or indirect evidence and required substantial extrapolation by an expert task force. All statements, therefore, should be considered conditional or provisional. The ACR is committed to updating this guidance document as new evidence emerges.
The rheumatology community lacks important knowledge on how to best maximize vaccine-related benefits. RMD patients exhibit high variability with respect to their underlying health condition, disease severity, treatments, degree of multimorbidity, and relationship with their specialist provider. These considerations must be considered when individualizing care.
Based on evidence published to date, the expected benefits of the COVID-19 vaccine outweigh the potential for vaccine harm in most RMD patients.
The future COVID landscape is uncertain with respect to vaccine effectiveness and safety, uptake, durability, mitigating societal behavior, and emerging viral strain variants. Clinicians nevertheless must act with their best judgement despite this highly uncertain and rapidly changing landscape.
The risk of deferring vaccination and thus failing to mitigate COVID-19 risk should be weighed against a possible blunted response to the vaccine if given under suboptimal circumstances. As a practical matter, this tension must be resolved in the context of imperfect prediction as to whether those circumstances may be transient, and a paucity of scientific evidence.
Both individual and societal considerations related to a limited vaccine supply should be considered in issuing vaccine guidance and making policy decisions. Given that context, simplicity should be the touchstone: to avoid confusion, improve implementation, and maintain scientific credibility.

RMD = rheumatic and musculoskeletal disease; mRNA = messenger RNA

Appendix Table 1: Examples of Monoclonal Antibodies Currently or Previously Available for the Prevention or Treatment of COVID-19

COVID-19 Monoclonal Antibodies	Route	Pre-Exposure Prophylaxis (PrEP)	Post-Exposure Prophylaxis	Treatment for active infection	Evidence for effectiveness vs. Omicron variant	EUA Status
Tixagevimab + Cilgavimab (Evusheld)[1]	**IM**	✓	**Ø**	**Ø**	✓	**Granted 12/8/21**
Sotrovimab[2]	**IV**	**Ø**	**Ø**	✓	✓	**Granted 5/26/21**
Bamlanivimab + Etesevimab	**IV**	**Ø**	✓	✓	**Ø**	**Granted 2/9/21; revoked 1/24/22[3]**
Casirivimab + Imdevimab (REGEN-COV)	**IV or SC**	**Ø**	✓	✓	**Ø**	**Granted 8/10/21; revoked 1/24/22[3]**

EUA = Emergency Use Authorization from the U.S. Food and Drug Administration; IM = intramuscular; IV = intravenous; SC = subcutaneous

(1) **Prevention of COVID-19:** Tixagevimab + Cilgavimab (Evusheld) is one example of a monoclonal available for **pre-exposure prophylaxis (PrEP)** against SARS-CoV-2 in a person who is moderately to severely immunocompromised and therefore may not mount an adequate immune response to COVID-19 vaccination (or for whom full vaccination is contraindicated). A large percentage of patients with rheumatologic conditions are unlikely to fully respond to COVID-19 vaccines due to immune suppressing medications, and PrEP offers such patients long-lasting preventive protection (6 months in the case of Tixagevimab + Cilgavimab) against SARS-CoV-2. It is not necessary to time the administration of PrEP in relation to the timing of immunosuppressive medications, and none need be held or delayed with relation to PrEP administration.

(2) **Treatment of acute COVID-19:** Sotrovimab is an example of a monoclonal antibody that is currently available for the treatment of outpatients with mild-to-moderate COVID-19 who have risk factors for progression to more severe disease. Such a medication is authorized for administration within 10 days of symptom onset, but it is most effective when given as soon as possible following diagnosis.

(3) **Revoked by FDA** based on available information including suggesting that U.S. variant susceptibility is limited given current U.S. regional variant frequency, infection, and exposure.

[+] **Appendix Table 2: History of Major Changes to ACR COVID Vaccine Guidance Statements in the Summary Tables (i.e., this online document) and Locations in the Published Manuscript Tables and Prose Where Guidance Was Revised**		
Provided guidance to hold acetaminophen and NSAIDs for 24 hours prior to vaccination, assuming disease is stable	Table 5 (Summary Table 3)	Version 2
Modified guidance for mycophenolate to hold for 1 week after each vaccine dose	Table 5 (Summary Table 3)	Version 2
Modified guidance for methotrexate to hold for 1 week after each of the 2 mRNA vaccine doses, and for 2 weeks after single-dose COVID vaccine	Table 5 (Summary Table 3)	Version 2
Citations added describing the attenuation of SARS-CoV-2 vaccine response observed in patients receiving mycophenolate, methotrexate, janus kinase inhibitors, and other immunomodulatory therapies	Prose accompanying Table 5	Version 2
Age restriction lowered to age 12	Footnote to Table 3 (Summary Table 2)	Version 3
Preference for mRNA vs. non-mRNA vaccines	Footnote to Table 3 (Summary Table 2)	Version 3
Need for continued preventive measures	Footnote to Table 3 (Summary Table 2)	Version 3
Preference for two-dose mRNA vaccine over single-dose vaccine in AIIRD patients	(Summary Table 2)	Version 4
Recommendation for booster vaccination in AIIRD patients	(Summary Table 2)	Version 4
Recognition of the FDA Emergency Use Authorization for use of post-exposure prophylaxis with casirivimab and imdevimab (REGEN-COV) for prevention of COVID-19 in AIIRD patients	(Summary Table 2)	Version 4
Recommended temporary interruption of oral calcineurin inhibitors at time of vaccination	(Summary Table 3)	Version 4
Recommendations for temporary treatment interruption of various immunomodulatory therapies at the time of receipt of a vaccine booster dose.	(Summary Table 3)	Version 4
Age restriction lowered to age 5	Footnote to Table 3	Version 4 Revised
Recommendation for supplemental (booster) dosing for mRNA and J&J vaccine recipients	(Summary Table 2)	Version 4 Revised
Preference for the same type of mRNA supplemental (booster) dose in patients previously completing either the Pfizer or Moderna mRNA vaccine series	(Summary Table 2)	Version 4 Revised
Recommendation for monoclonal antibody therapy with REGEN-COVID as either prevention (i.e., post-exposure prophylaxis) or as treatment for high-risk patients	(Summary Table 2)	Version 4 Revised
Complete revision of immunomodulatory medication recommendations regarding timing in relation to	(Summary Table 3)	Version 4 Revised

COVID-19 vaccine series and supplemental (booster) dosing		
Terminology distinction made between additional primary (supplemental) doses and booster doses.	Throughout document	Version 4 Revised
Guidance on supplemental vaccine dosing to follow CDC recommendations for immunocompromised individuals	**(Summary Table 2)**	Version 5
Recommendation to booster vaccine dosing to follow CDC recommendations for immunocompromised individuals	**(Summary Table 2)**	Version 5
Revisions to existing and revised recommendations for pre-exposure and post-exposure monoclonal antibody prophylaxis for high-risk individuals, conditional on FDA licensure or EUA	**(Summary Table 2) (Summary Appendix Table 1)**	Version 5
Modification to guidance for IVIG to make no timing alterations to vaccination or IVIG administration	**(Summary Table 3)**	Version 5

Recommendations updated April 28, 2021
Link to Version 1 manuscript added May 24, 2021
Link to Version 2 manuscript added June 15, 2021
Recommendations updated June 19, 2021
Link to Version 3 manuscript added August 4, 2021
Recommendations updated August 19, 2021
Recommendations updated October 27, 2021
Recommendations updated December 15, 2021
Recommendations updated January 28, 2022
Recommendations updated February 2, 2022
Link to version 4 and version 5 manuscripts pending

***** How to cite this article:**
Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases – Version 1. Arthritis Rheumatol 2021. https://onlinelibrary.wiley.com/doi/10.1002/art.41734

****** How to cite this article:**
Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases – Version 2. Arthritis Rheumatol 2021. https://onlinelibrary.wiley.com/doi/full/10.1002/art.41877

******* How to cite this article:**
Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases – Version 3. Arthritis Rheumatol 2021. https://onlinelibrary.wiley.com/doi/10.1002/art.41928