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2022 American College of Rheumatology Guideline for Vaccinations in Patients With Rheumatic and Musculoskeletal Diseases

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Bass had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Abstract

Objective.—To provide evidence-based recommendations on the use of vaccinations in children and adults with rheumatic and musculoskeletal diseases (RMDs).

Methods.—This guideline follows American College of Rheumatology (ACR) policy guiding management of conflicts of interest and disclosures and the ACR guideline development process, which includes the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. It also adheres to the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria. A core leadership team consisting of adult and pediatric rheumatologists and a guideline methodologist drafted clinical population, intervention, comparator, outcomes (PICO) questions. A review team performed a systematic literature review for the PICO questions, graded the quality of evidence, and produced an evidence report. An expert Voting Panel reviewed the evidence and formulated recommendations. The panel

included adult and pediatric rheumatology providers, infectious diseases specialists, and patient representatives. Consensus required ≥70% agreement on both the direction and strength of each recommendation.

Results.—This guideline includes expanded indications for some vaccines in patients with RMDs, as well as guidance on whether to hold immunosuppressive medications or delay vaccination to maximize vaccine immunogenicity and efficacy. Safe approaches to the use of live attenuated vaccines in patients taking immunosuppressive medications are also addressed. Most recommendations are conditional and had low quality of supporting evidence.

Conclusion.—Application of these recommendations should consider patients' individual risk for vaccine-preventable illness and for disease flares, particularly if immunosuppressive medications are held for vaccination. Shared decision-making with patients is encouraged in clinical settings.

INTRODUCTION

Rheumatic and musculoskeletal diseases (RMDs) (1,2) and immunosuppressive medications used to treat them place patients at higher risk of vaccine-preventable infections and of more serious complications of infection. Vaccines have long been used to reduce illness from common viral and bacterial pathogens, and standardized vaccine schedules for children and adults have been widely adopted for use in both healthy people and those with chronic medical conditions (3,4). However, the immunogenicity and safety of vaccines may differ in patients with RMDs compared to the general population, and patients with RMDs may benefit from modified vaccine indications and/or adjustments to vaccination or medication schedules. Issues related to vaccination and medication management at the time of vaccination apply across diseases, and thus, this guideline is meant to help in the management of vaccines for all children and adults with RMDs in the US. The target audience is limited to rheumatology providers in the US because the epidemiology of vaccine-preventable infections and the availability of specific vaccines vary across the globe. However, providers in other countries may also find the guideline useful. A list of specific medications, vaccinations, and RMDs addressed in this guideline is found in Table 1, and a glossary of terms commonly used in this guideline can be found in Table 2.

Avacopan and bimekizumab, the pneumococcal vaccines PCV15 and PCV20, and the smallpox/monkeypox vaccine were not included in the formal evidence review because they were not approved at the time of the project plan. Antipyretic medications such as nonsteroidal antiinflammatory drugs and acetaminophen were also not included. Although a few randomized controlled trials (RCTs) have demonstrated blunted antibody responses with antipyretics, this was seen after primary vaccination only, and not after booster (5) or influenza vaccination (6). Observational studies also suggest that they have minimal-to-no impact on antibody responses to vaccination (5,7). Vaccinations against COVID-19 are not included in this guideline because, given the fast-changing nature of the pandemic and the COVID-19–related literature, there was concern that recommendations would be obsolete well before guideline publication. COVID-19 vaccinations will be incorporated into a future guideline update once the pertinent literature has stabilized. We refer readers to the American College of Rheumatology (ACR) COVID-19 vaccine guidance (8) and

to the Centers for Disease Control and Prevention (CDC) website (9) for information on COVID-19 vaccines for patients with compromised immunity. Finally, we refer readers to the Advisory Committee on Immunization Practices (ACIP) (10) and the American Academy of Pediatrics (AAP) (11) vaccination guidelines for any other topics not addressed herein. This study did not involve human subjects, and therefore, approval from Human Studies Committees was not required.

The 2022 ACR guideline for vaccination in adults and children with RMDs highlights the following: 1) pneumococcal vaccination should be administered to all RMD patients taking immunosuppressive medication; 2) recombinant zoster vaccination is recommended for RMD patients >18 years of age taking immunosuppressive medication; 3) methotrexate should be held for 2 weeks after influenza vaccination if disease activity allows; 4) seasonal influenza vaccination should be administered to RMD patients even if their disease is active, they are taking high-dose glucocorticoids, and/or they are taking rituximab; 5) in RMD patients taking rituximab, vaccines other than for influenza should be administered at least 6 months after the last rituximab dose; and 6) infants exposed to tumor necrosis factor inhibitors (TNFi) in utero should receive rotavirus vaccination in the first 6 months of life.

METHODS

This guideline follows ACR policy guiding management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) and the ACR guideline development process, which includes Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (12,13), and adheres to the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria (14). Supplementary Appendix 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42386, includes a detailed description of the methods. Briefly, the guideline team drafted clinical population, intervention, comparator, outcomes (PICO) questions (see Supplementary Appendix 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42386). The literature review team performed a systematic literature review for the PICO questions, graded the quality of evidence (high, moderate, low, very low), and produced the evidence report (see Supplementary Appendix 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42386). An expert Voting Panel reviewed the evidence report and then formulated and voted on recommendations. Additionally, a virtual Patient Panel reviewed the evidence and provided patient perspectives and preferences for consideration by the Voting Panel. The Patient Panel consisted of 9 patients with a variety of adult and pediatric RMDs and was moderated by a member of the core team (EC).

Voting Panel consensus required ≥70% agreement on both the direction (for or against) and strength (strong or conditional) of each recommendation, as per ACR practice. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when costs are expected to impact the

decision. Thus, for conditional recommendations, incorporation of patient preferences is particularly essential, acknowledging that patient preferences are an important part of all clinical decision-making. Rosters of the Core Leadership Team, Literature Review Team, Voting Panel, and Patient Panel are included in Supplementary Appendix 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42386.

The following guiding principles were used in this guideline: 1) indicated vaccinations should be given to patients whenever possible; 2) this guideline is complementary to recommendations from the ACIP (10) and the AAP (15); 3) the decision to hold a medication before or after vaccination should consider the patient's disease, disease activity, and risk for vaccine-preventable infection; and 4) shared decision-making with patients is a key component of any vaccination strategy.

RESULTS/RECOMMENDATIONS

Expanded indications for specific vaccines in patients with RMDs receiving immunosuppression

Influenza vaccination—For patients with RMD age ≥65 years and patients with RMD age >18 years and <65 years who are taking immunosuppressive medication, giving high-dose or adjuvanted influenza vaccination is conditionally recommended over giving regular-dose influenza vaccination.

Any influenza vaccine is preferred over no influenza vaccine, and vaccination "today" is preferred over delay. Therefore, if high-dose or adjuvanted influenza vaccine is not available in the clinic during a patient visit when influenza vaccination is indicated, then standard-dose influenza vaccine should be administered. This caveat also applies in instances when insurance restrictions may preclude administration of high-dose or adjuvanted influenza vaccination to patients <65 years of age.

High-dose influenza vaccine is a quadrivalent vaccine containing 4 times the antigen as the standard-dose vaccine. Two RCTs in rheumatoid arthritis (RA) patients showed higher seroconversion rates in younger patients receiving high-dose vaccination compared to standard-dose vaccination with no safety signal (16,17). The adjuvanted influenza vaccine is a standard-dose quadrivalent vaccine containing the MF59 adjuvant, which elicits a strong antigenic response without the need for a higher antigen dose. No studies of the adjuvanted influenza vaccination in RMD patients age <65 years were identified in the literature search, but there have been no safety issues seen with adjuvants in general, although they may be associated with greater reactogenicity (18).

Pneumococcal vaccination—For patients with RMD age <65 years who are taking immunosuppressive medication, pneumococcal vaccination is strongly recommended.

Patients with RMDs taking immunosuppressive medication may be at increased risk of pneumococcal infection (19,20). Multiple observational studies have evaluated the prime boost method of pneumococcal vaccination, with a pneumococcal conjugate vaccine (PCV13 or PCV15), followed 2 months later by a dose of the pneumococcal

polysaccharide vaccine (PPSV23). A single-dose PCV20 vaccine is now approved in the US (21) and is likely to supplant this 2-dose strategy in the not-too-distant future, at least in adults. PCV15 and PCV20 polysaccharide conjugates are not currently approved for use in children in the US; but this too may soon change. The CDC currently recommends PCV15 followed by PPSV23 one year later, or PCV20, for adults <65 years taking immunosuppressive medications who were not previously vaccinated against pneumococcus, however, we recommend reference to CDC guidelines when choosing a specific pneumococcal vaccination strategy because this area is rapidly changing (21).

There are few studies evaluating the impact of disease-modifying antirheumatic drugs (DMARDs) on conjugate pneumococcal vaccines. The ACIP recommends administering pneumococcal vaccination to individuals age >18 years with certain chronic medical conditions and those taking immunosuppressive medication (10,22). The CDC and AAP recommend the primary PCV13 series to all children <2 years of age and PPSV23 vaccination to children age ≥2 years with underlying medical conditions (15).

Recombinant varicella-zoster virus (VZV) vaccination—For patients with RMD age >18 years who are taking immunosuppressive medication, administering the recombinant VZV vaccine is strongly recommended.

Patients with RMDs such as systemic lupus erythematosus (SLE) and RA are at higher risk of herpes zoster than older adults recommended for vaccination (23). Although the literature search identified no publications that specifically addressed recombinant VZV vaccination in patients with RMDs who are <50 years of age, this vaccine has been shown to be safe and effective in immunosuppressed patients undergoing renal transplantation (24) and autologous stem cell transplantation (25) and in patients with hematologic malignancies, many of whom are <50 years of age (26,27). The ACIP recommends recombinant VZV vaccination for individuals >18 years and <50 years of age who are immunocompromised and for the general public age ≥50 years (10). One retrospective study demonstrated mild disease flares in some patients around the time of vaccination (28), and reactogenicity is common with this vaccine (26).

Human papillomavirus (HPV) vaccination—For patients with RMD age >26 years and <45 years who are taking immunosuppressive medication and not previously vaccinated, vaccination against HPV is conditionally recommended.

Patients taking immunosuppressive medication may be at increased risk of cervical dysplasia and cervical cancer (29–33). Two studies of young patients with SLE (mean age 38 years and 26 years in the 2 studies, respectively) demonstrated that vaccination against HPV was immunogenic and well tolerated (34,35). The ACIP recommends HPV vaccination for individuals ages 11–26 years. For those ages 26–45 years who have not been previously vaccinated, ACIP recommends HPV vaccination based on shared decision-making (10). The benefits of vaccination after age 45 years diminish due to the greater likelihood of previous exposure to HPV.

Whether to hold immunosuppressive medication at the time of non–live attenuated vaccination to maximize vaccine immunogenicity, although holding medications could be associated with disease flare (Table 3).

Methotrexate—For patients with RMD, *holding* methotrexate for 2 weeks after influenza vaccination is conditionally recommended, assuming disease activity allows.

For patients with RMD, continuing immunosuppressive medications other than methotrexate around the time of influenza vaccination is conditionally recommended.

For patients with RMD, continuing immunosuppressive medications around the time of other (non-influenza) non–live attenuated vaccinations is conditionally recommended.

Many observational studies (36,37) suggest that methotrexate significantly blunts but does not completely abrogate the immunogenicity of influenza vaccination. Two RCTs demonstrated a beneficial impact of holding methotrexate around the time of influenza vaccination on vaccine immunogenicity (38,39). Assessment of flare risk and shared decision-making with the patient is recommended when deciding whether methotrexate should be held. Non-rheumatology providers (e.g., general pediatricians and internists) are encouraged to give influenza vaccination even if they are unsure as to whether to hold methotrexate, and then to consult with the patient's rheumatologist, rather than miss a vaccination opportunity. The literature review did not identify any studies that addressed holding medications in the context of vaccines other than for influenza. However, 2 studies published after completion of the literature review suggested that holding methotrexate at the time of COVID-19 vaccination is associated with greater vaccine immunogenicity (40,41).

The literature review identified no studies that directly addressed the impact of holding medications other than methotrexate at the time of influenza vaccination. Two RCTs performed in patients initiating TNFi versus placebo demonstrated similar responses to influenza vaccination in the 2 arms (42,43). Data on other biologic DMARDs and their relationship to influenza vaccine responses are much more limited (44–47).

Rituximab—For patients with RMD receiving rituximab, administering influenza vaccination on schedule is conditionally recommended rather than deferring vaccination until the next rituximab administration is due.

For patients with RMD receiving rituximab, *deferring* non–live attenuated vaccinations, other than influenza vaccination, until the next rituximab administration is due, and *delaying* rituximab for 2 weeks after vaccination, is conditionally recommended.

Influenza vaccine responses are greater when the vaccine is administered later rather than earlier after rituximab (48–50). Rituximab has also been shown to blunt responses to pneumococcal polysaccharide PPSV23 vaccination (51,52). Because of the seasonal nature of influenza, influenza vaccination is conditionally recommended to be given on schedule to patients receiving rituximab. For other non–live attenuated vaccinations, deferring vaccination until the next rituximab dose will improve vaccine immunogenicity.

However, patients could also be vaccinated in the interest of acquiring some immunity and then revaccinated later (influenza vaccination could also be repeated using this same rationale). Whenever possible, vaccinations should be administered prior to rituximab initiation. Rituximab should be delayed for at least 2 weeks after any vaccination to allow time for the patient to develop an immune response, assuming that disease activity allows.

Whether to administer non–live attenuated vaccinations to patients receiving glucocorticoids or with active disease (Table 4).

Glucocorticoids—Whether to administer non–live attenuated vaccinations to patients taking glucocorticoids or defer vaccination to a later time point to maximize vaccine immunogenicity.

For patients with RMD who are taking the equivalent of prednisone ≤10 mg daily, administering any non–live vaccinations is strongly recommended.

For patients with RMD who are taking the equivalent of prednisone >10 mg daily but <20 mg daily, administering any non–live attenuated vaccinations is conditionally recommended.

For patients with RMD taking the equivalent of prednisone ≥20 mg daily, administering influenza vaccination is conditionally recommended.

For patients with RMD who are taking the equivalent of prednisone ≥20 mg daily, *deferring* non–live attenuated vaccinations, other than influenza vaccination, until glucocorticoids are tapered to the equivalent of prednisone <20 mg daily is conditionally recommended.

Most studies that have compared prednisone <10 mg daily to prednisone ≥10 mg daily found that the higher dosages did reduce influenza vaccine immunogenicity (53–55). Several studies that defined high-dose glucocorticoids as prednisone ≥20 mg daily observed that they blunted patients' vaccine response (56–58). Two studies that examined glucocorticoid dosage as a continuous variable identified a dose–response relationship while suggesting against a specific dose threshold (57,58). Evidence for the impact of glucocorticoids on responses to other vaccines is less consistent (59–61). For some vaccines, humoral responses can be measured and revaccination considered in those with an inadequate response.

Given the importance of timely influenza vaccination, a conditional recommendation was made to administer influenza vaccination to patients receiving the equivalent of prednisone ≥20 mg daily. For vaccines other than for influenza, a conditional recommendation was made to delay vaccination until the dose is lower to maximize vaccine efficacy. It is understood, however, that some patients may not be able to delay, e.g., children who require vaccination for school entry.

Disease activity—Whether to defer vaccination in patients with high disease activity to maximize vaccine immunogenicity and/or avoid worsening disease activity.

For patients with RMD, giving non–live attenuated vaccinations is conditionally recommended regardless of patients' disease activity.

Patients with RMD often express concern about whether vaccination can induce a disease flare, but the vast majority of studies failed to show any increased rate of flare after influenza vaccination. The results were similar for other vaccinations, although the quality of the evidence was low. Strong concerns, however, were expressed among the Patient Panel about the potential for vaccines to cause a disease flare, and shared decision-making is particularly important in this setting. Most studies suggest that increased disease activity does not impact vaccine immunogenicity (53,62), although one study did show lower seroconversion rates in pediatric lupus patients with a Systemic Lupus Erythematosus Disease Activity Index score of >8 who were vaccinated against influenza (57).

Managing immunosuppressive therapy at the time of live attenuated vaccination to avoid vaccine-associated illness (Table 5).

For patients with RMD who are taking immunosuppressive medication, *deferring* live attenuated vaccines is conditionally recommended.

For patients with RMD, *holding* immunosuppressive medication for an appropriate period before and 4 weeks after live attenuated virus vaccination is conditionally recommended.

For some live attenuated virus vaccines, such as for oral polio, oral typhoid, and influenza, there are inactivated alternatives that can be safely given to RMD patients taking immunosuppressive medication.

Conventional DMARDs.: Two observational studies in patients with RMDs who were only taking conventional DMARDs and/or prednisone <20 mg daily at the time they received the yellow fever vaccine observed no cases of infection (63,64). Similarly, in a retrospective cohort study of patients with juvenile idiopathic arthritis (JIA) taking methotrexate and vaccinated against measles, mumps, and rubella (MMR), none developed vaccine-associated disease (65). Some pediatric rheumatologists do recommend giving live attenuated virus vaccine boosters (66) to children receiving low-dose immunosuppression when the child is likely to be taking the medication long term and when the risk of flare when not receiving immunosuppression is high, especially in areas with low community vaccination rates and/or during outbreaks (67). The AAP Red Book (15) and the Infectious Diseases Society of America (68) define low-level immunosuppression as methotrexate ≤0.4 mg/kg/week, azathioprine ≤3 mg/kg/day, prednisone <20 mg/day (or <2 mg/kg/day for patients weighing <10 kg), or alternate-day glucocorticoid therapy (68).

Biologic DMARDs.: In a large RCT of RMD patients taking TNFi who were given the live attenuated VZV vaccine, there were no confirmed cases of varicella infection in either the vaccine or placebo group during 1 year of follow-up (69). Similarly, in an observational study of patients with Kawasaki disease who received vaccines against rotavirus and/or MMR plus varicella within 90 days prior to a single dose of infliximab, none experienced any serious infections (70). Finally, in a study of RA patients given a yellow fever booster 1 month after their last dose of infliximab, none developed symptoms of yellow fever (71).

In contrast, in a very small retrospective study based on an email survey to pediatric and adult rheumatologists and immunologists that reported on 17 children with

autoinflammatory disorders or systemic JIA taking interleukin-1 or interleukin-6 receptor inhibitors and who were given a variety of live attenuated vaccinations, 3 of 17 patients developed vaccine-associated infection, and 7 of 17 patients experienced disease flares (72).

JAK inhibitors.: Cutaneous vaccine-strain varicella infection developed in 1 of 55 RA patients given a single dose of the live attenuated VZV vaccine 2–3 weeks prior to tofacitinib initiation in the context of an RCT. Later testing demonstrated that the study participant lacked prevaccination immunity to VZV (73). Complete lack of immunity to varicella is rare in adults in the US, where the prevalence of varicella seropositivity is 98% in adults (74).

Intravenous immunoglobulin (IVIG).: Antiviral antibodies contained in IVIG can interfere with replication of live attenuated vaccines and reduce their efficacy (75). The CDC recommends a delay of 8–11 months (depending on IVIG dose) between receipt of high-dose IVIG and live attenuated virus vaccination (76). However, there will be situations, such as during a measles outbreak, when earlier vaccination is preferred over delay because some immunity will be preferred over none in that setting.

Specific recommendations for holding medications if live attenuated vaccines are given.: Although the evidence around the safety of conventional DMARDs and TNFi at the time of live attenuated virus vaccination is reassuring, the total number of RMD patients who have been studied is small, and the Voting Panel conditionally recommended against administering live attenuated virus vaccines to patients receiving those agents as well as other forms of immunosuppression. For patients who do need to receive live attenuated vaccines, specific recommendations for holding immunosuppressive medications around the time of vaccination can be found in Table 5.

For slow-acting conventional DMARDs, a prevaccination hold time of 4 weeks was chosen to reflect their prolonged duration of action. However, direct evidence for the optimal hold time is lacking. For most biologic DMARDs, a hold time of 1 dosing interval before live attenuated vaccine administration is recommended.

The number of RMD patients who are taking immunosuppressive medications at the time that they need live attenuated virus vaccines is small. However, very young children, especially those with autoinflammatory disorders, may require biologic DMARDs before their primary vaccination series is complete. In these children, the risk associated with a disease flare may be considerably higher than the risk associated with the vaccine preventable illness (72). Children with autoinflammatory disorders also often require lifelong anticytokine therapy, and there may never be an opportunity to catch up on missed vaccinations later. For these children, shorter medication hold times can be considered if live attenuated virus vaccination is critical and cannot be delayed. Shared decision-making with the child’s parents/guardians is important in this setting, and they should be alerted to the signs and symptoms of attenuated vaccine-associated infection.

The recommendation to hold immunosuppressive medications for 4 weeks after live attenuated vaccination is conservative. Typically, the duration of viremia (live virus

circulating in the blood) after live attenuated vaccination is 2 weeks, although it can be longer in some patients (77). Viremia is more prolonged after primary vaccination than after booster vaccinations (77). Medication hold times after vaccination can be shortened if vaccination is critical and the risk of a disease flare when the patient is not receiving immunosuppression is high.

Close contacts of immunosuppressed patients should receive all age-appropriate vaccination (with the exception of smallpox) to avoid the vaccine-preventable diseases, as recommended by the ACIP (78). The ACIP also notes that no specific precautions are needed except if a household contact develops a rash after varicella vaccination, in which case direct contact should be avoided until the rash resolves (78). They also reinforce the recommendation to household members to wash their hands after diaper changing when an infant has received a rotavirus vaccine (78).

When to administer rotavirus vaccine to infants with second- and/or third-trimester antenatal exposure to biologic DMARDs in utero (Table 6).

For neonates/infants with second- and/or third-trimester antenatal exposure to TNFi, giving live attenuated rotavirus vaccine within the first 6 months of life is conditionally recommended.

For neonates/infants with second- and/or third-trimester antenatal exposure to rituximab, *delaying* live attenuated rotavirus vaccine until >6 months of age is conditionally recommended.

Vaccination against rotavirus typically occurs at 2 and 4 months, or at 2, 4, and 6 months. Rotavirus is rare in the US because of widespread immunization, and for this reason, the AAP recommends delaying rotavirus vaccination for 12 months after any in utero exposure to biologic DMARDs (except for certolizumab, which does not cross the placenta) (15). Three observational studies encompassing 58 children exposed to biologic DMARDs (most taking TNFi) who received live rotavirus vaccines reported no clear adverse events (79–81). Only minimal amounts of infliximab have been detected in the breast milk of treated patients (82).

The literature review identified no data on the effect of in utero rituximab exposure on later vaccine responses. Rituximab is a chimeric IgG1 molecule that can cross the placenta, and it has been associated with low or absent B lymphocyte levels in newborns who were exposed during the second or third (but not the first) trimester (83). Most reports demonstrate B cell recovery in these infants within 6 months after birth (83). Extrapolating from vaccine responses in adults treated with rituximab (48–50), infants exposed to rituximab are unlikely to respond to vaccination until 6 months postexposure. Although delayed rotavirus vaccine administration has been associated with an increased risk of intussusception, this complication remains quite rare (84).

After giving birth, most RMD patients turn to their general pediatrician rather than to their adult rheumatology provider for infant vaccination recommendations, and pediatricians may not be aware of the impact of in utero medication exposure on vaccine safety and

immunogenicity. Therefore, recommendations regarding infant rotavirus vaccination after in utero exposure to either TNFi or rituximab should be discussed with the pregnant RMD patient prior to delivery. Specifically, the pregnant patient should be educated as to the fact that medications that cross the placenta may affect vaccination schedules for their infants. A copy of the current vaccine guideline summary (https://www.rheumatology.org/Portals/0/Files/Vaccinations-Guidance-Summary.pdf) may serve as a useful resource for the pregnant RMD patient to share with their pediatrician in advance of delivery.

Whether to give multiple vaccinations to patients with RMD on the same day.

For patients with RMD, giving multiple vaccinations on the same day rather than giving each individual vaccination on a different day is conditionally recommended.

Administering >1 vaccination on a single day is a routine practice in both pediatric and adult medicine that is supported by the CDC in order to avoid a missed vaccination opportunity (85). Patient representatives on the Voting Panel felt that shared decision-making was important in this instance due to their concerns about the potential for reactogenicity or disease flare.

A summary of the guideline recommendations, associated PICO questions, and level of evidence can be found in Table 7.

DISCUSSION

This is the first guideline to address vaccination strategies across the entire adult and pediatric RMD spectrum. An underlying principle in this guideline is that patients should be vaccinated, and that missed vaccination opportunities should be avoided or minimized. This is particularly true regarding influenza vaccination, which is administered seasonally and is recommended for RMD patients even if their disease activity is high, they are taking high-dose glucocorticoids, and/or are taking rituximab. The Voting Panel generally favored simple recommendations to encourage vaccination and foster guideline adherence. There are few studies assessing the immunogenicity and safety of specific vaccines in relation to specific immunosuppressive medications, and there are virtually no studies assessing the impact of holding medications around the time of vaccination, particularly for vaccines other than for influenza. Therefore, many of the recommendations are conditional and apply across diseases, vaccines, medications, and age groups. Because of the low quality of the evidence, shared decision-making between clinicians and patients/parents/guardians is particularly important for the vaccination strategies presented here. These recommendations do not supersede clinical judgement.

Most recommendations in this guideline are aimed at maximizing vaccine immunogenicity because the literature revealed few vaccine safety signals, at least regarding non-live vaccinations. Many vaccines are required for school entry to protect not only the health of the individual but also that of the broader community. Public health requirements may supersede some recommendations made here. Insurance barriers could inhibit implementation of these recommendations, such as to administer high dose or adjuvanted influenza vaccine or recombinant VZV to RMD patients <65 years of age taking

immunosuppressive medications. In such instances, this guideline could be used as a resource to aid in prior authorization.

Not included in this guideline are recommendations for COVID-19 vaccination in patients with RMD. Readers can refer to the CDC for the most up-to-date recommendations for COVID-19 vaccination, including for patients taking immunosuppressive medication (9). Recommendations about holding immunosuppressive medications at the time of non–live attenuated virus vaccination in this guideline (Table 3) differ from those recommended around the time of COVID-19 vaccination in the ACR COVID-19 vaccine guidance (8). This is because prior to the introduction of COVID-19 vaccines in late 2020, there was little population-level immunity to the SARS–CoV-2 virus, and maximizing vaccine efficacy was a public health imperative. In contrast, when considering routine vaccinations, the desire to avoid an RMD flare weighs more heavily in the balance. Therefore, there are very few instances where this guideline recommends holding medication at the time of non–live attenuated virus vaccination. Studies that demonstrate diminished vaccine responses in RMD patients receiving immunosuppression (other than rituximab) generally demonstrate diminished, but not completely abrogated, responses.

Finally, the literature review demonstrated that much more evidence is needed to guide practice in this area. Knowledge gaps where further research is needed are as follows: 1) standardization of trial design and outcome measures to test the efficacy and durability of response to all vaccines across all age groups; 2) safety of primary and booster live attenuated virus vaccination in children taking methotrexate and/or biologic DMARDs; 3) assessment of the immunogenicity, reactogenicity, and disease flares following standard-dose, high-dose, and adjuvanted influenza vaccination, recombinant VZV vaccination, and primary and booster COVID-19 vaccination in RMD patients taking immunosuppressive medication; and 4) RCTs to test the safety and efficacy of holding DMARDs around the time of vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Guideline scope*

Medications		Vaccines†		
Immunosuppressive	**Nonimmunosuppressive**	**Non–live attenuated**	**Live attenuated**	**Rheumatic and musculoskeletal disorders**
Glucocorticoids Prednisone Methylprednisolone Dexamethasone Hydrocortisone csDMARDs Methotrexate Leflunomide Azathioprine Mycophenolate mofetil/mycophenolic acid Calcineurin inhibitors (cyclosporine, tacrolimus, voclosporin) Cyclophosphamide bDMARDs TNF inhibitors (etanercept, adalimumab, certolizumab, golimumab, infliximab) IL-6R inhibitors (tocilizumab, sarilumab) IL-17 inhibitors (secukinumab, ixekizumab) IL-12/23 inhibitors (ustekinumab) IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab) IL-1 inhibitors (anakinra, canakinumab, rilonacept) T cell costimulation inhibitor (CTLA4-Ig/abatacept) B cell–depleting agents (rituximab, ocrelizumab, obinutuzumab) BLyS/BAFF inhibitors (belimumab, tabalumab) Interferon-α receptor inhibitor (anifrolumab) tsDMARDs JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib, ruxolitinib)	Hydroxychloroquine Sulfasalazine Colchicine Apremilast Denosumab IVIG	Seasonal influenza Standard dose, high dose, adjuvanted Pneumococcal PPSV23, PCV13‡ Other Hemophilus influenza Hepatitis A Hepatitis B Human papillomavirus Inactivated polio Meningococcus B Meningococcus ACWY Tetanus toxoid/Td/Tdap Typhoid (injectable) Zoster subunit	Influenza (intranasal) MMR Rotavirus Typhoid (oral) Varicella Yellow fever Zoster	Inflammatory arthropathies Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis Spondyloarthritis Enthesitis-related arthritis IBD-associated arthritis Juvenile idiopathic arthritis Connective tissue diseases Systemic lupus erythematosus Sjögren's syndrome Systemic sclerosis Idiopathic inflammatory myopathies Mixed connective tissue disease Undifferentiated connective tissue disease Antiphospholipid antibody syndrome Vasculitides Granulomatosis with polyangiitis Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis Giant cell arteritis Polyarteritis nodosa Takayasu arteritis Cryoglobulinemic vasculitis Relapsing polychondritis Behçet's disease Kawasaki disease IgA vasculitis (Henoch-Schönlein) Primary CNS vasculitis Goodpasture's syndrome (anti-GBM) Cogan's syndrome Cutaneous small vessel vasculitis Rheumatoid vasculitis Urticarial vasculitis Other inflammatory disorders Sarcoidosis Adult-onset Still's disease Polymyalgia rheumatica Gout Pseudogout IgG4-related disease Autoinflammatory disorders

[*] MMR = measles, mumps, and rubella (vaccine); PPSV23 = pneumococcal polysaccharide vaccine; PCV13 = pneumococcal conjugate vaccine; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; IVIG = intravenous immunoglobulin; IBD = inflammatory bowel disease; bDMARDs = biologic DMARDs; TNF = tumor necrosis factor; IL-6R = interleukin-6 receptor; BLyS = B lymphocyte stimulator; tsDMARDs = targeted synthetic DMARDs; CNS = central nervous system; anti-GBM = anti–glomerular basement membrane (disease).

[†] COVID-19 vaccines were not included in this guideline because of the fast-changing face of the pandemic and related literature.

[‡] The recently approved pneumococcal vaccines, PCV15 and PCV20, were not included in the evidence review but are discussed in the text with reference to current Centers for Disease Control and Prevention guidelines.

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Table 2.

Glossary of terms

Term	Definition
Adjuvant	An ingredient used in some vaccines that helps create a stronger immune response in patients receiving the vaccine
Immunogenicity	The ability of a vaccine to elicit an immune response
Reactogenicity	Typical symptoms (e.g., fever, sore arm, muscle aches) that occur shortly (days) after vaccine administration either at the site of vaccination or systemically
Seroconversion	Development of antibodies to a pathogen, elicited by a vaccine (or infection), in the blood of an individual who previously did not have detectable antibodies
Seroprotection	An antibody level capable of protecting against infection or disease
Titer	Numerical value indicating the level of antibody against a particular pathogen

Table 3.

Medication management at the time of non–live attenuated vaccine administration

	Influenza vaccination	Other non–live attenuated vaccinations
Methotrexate	Hold methotrexate for 2 weeks *after* vaccination *	Continue methotrexate
Rituximab	Continue rituximab †	Time vaccination for when the next rituximab dose is due, and then hold rituximab for at least 2 weeks after vaccination
Immunosuppressive medications other than methotrexate and rituximab	Continue immunosuppressive medication	Continue immunosuppressive medication

= Conditional recommendation.

* Hold only if disease activity allows. Non-rheumatology providers, e.g., general pediatricians and internists, are encouraged to give the influenza vaccination and then consult with the patient's rheumatology provider about holding methotrexate to avoid a missed vaccination opportunity.

† Give influenza vaccination on schedule. Delay any subsequent rituximab dosing for at least 2 weeks after influenza vaccination if disease activity allows.

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Table 4.

Whether to give or defer non–live attenuated vaccinations in patients taking glucocorticoids regardless of disease activity

	Influenza vaccination	Other non–live attenuated vaccinations
Prednisone ≤10 mg daily *	Give	Give
Prednisone >10 mg and <20 mg *	Give	Give
Prednisone ≥20 mg daily *	Give	Defer †

= Strong recommendation.

= Conditional recommendation.

* Or the equivalent dose of any other glucocorticoid formulation, or the equivalent pediatric dose.

† Defer vaccination until glucocorticoids are tapered to the equivalent of prednisone <20 mg daily.

Table 5.

Immunosuppressive medication management at the time of live attenuated virus vaccine administration*

	Hold before live attenuated virus vaccine administration	Hold after live attenuated virus vaccine administration
Glucocorticoids†	4 weeks	4 weeks
Methotrexate, azathioprine‡	4 weeks	4 weeks
Leflunomide, mycophenolate mofetil, calcineurin inhibitors, oral cyclophosphamide	4 weeks	4 weeks
JAK inhibitors	1 week	4 weeks
TNF, IL-17, IL-12/23, IL-23, BAFF/BLyS inhibitors	1 dosing interval§	4 weeks
IL-6 pathway inhibitors	1 dosing interval¶	4 weeks
IL-1 inhibitors		
Anakinra	1 dosing interval¶	4 weeks
Rilonacept	1 dosing interval¶	4 weeks
Canakinumab	1 dosing interval¶	4 weeks
Abatacept	1 dosing interval§	4 weeks
Anifrolumab	1 dosing interval§	4 weeks
Cyclophosphamide, intravenous	1 dosing interval§	4 weeks
Rituximab	6 months	4 weeks
IVIG#		
300–400 mg/kg	8 months	4 weeks
1 gm/kg	10 months	4 weeks
2 gm/kg	11 months	4 weeks

*TNF = tumor necrosis factor; IL = interleukin; BLyS = B lymphocyte stimulator; IVIG = intravenous immunoglobulin.

†For patients taking the equivalent of prednisone <20 mg/day or <2 mg/kg/day for patients weighing <10 kg or alternate-day glucocorticoid therapy (i.e., “low-level immunosuppression” [15,68]), these low doses can be continued if vaccination is critical and the risk of a disease flare or adrenal insufficiency when the patient is not taking glucocorticoids is high.

‡For patients taking methotrexate ≤0.4 mg/kg/week or azathioprine ≤3 mg/kg/day (“low-level immunosuppression” [15,68]), hold times can be shortened if vaccination is critical and the risk of a disease flare when the patient is not taking immunosuppression is high.

§For medications with >1 dosing interval approved by the Food and Drug Administration, the longest interval should be chosen (e.g., hold subcutaneous adalimumab for 2 weeks, although it can be dosed every 1 or every 2 weeks).

¶In children with autoinflammatory disorders or systemic juvenile idiopathic arthritis in whom the risk of disease flare if biologic disease-modifying antirheumatic drugs are held is very high, shorter hold times can be considered if live attenuated vaccination is critical.

#The recommendation to hold IVIG prior to vaccination is designed to enhance vaccine efficacy, not safety. In some situations, such as during a measles outbreak, earlier vaccination would be preferred over delay.

Table 6.

When to administer live attenuated rotavirus vaccination to infants exposed to immunosuppressive medications in utero*

Antenatal drug exposure in second or third trimester	Within the first 6 months of life	After 6 months of life
TNFi	Give rotavirus vaccine	–
Rituximab	Do not give rotavirus vaccine	Give rotavirus vaccine

= Conditional recommendation.

*TNFi = tumor necrosis factor inhibitor.

Table 7.

Summary of recommendations *

Recommendations	Level of evidence †	PICO	Evidence table page numbers
Expanded indications for specific vaccines in patients with RMDs receiving immunosuppression			
Influenza vaccination			
For patients with RMD age ≥65 years and patients with RMD age >18 and <65 years who are taking immunosuppressive medication, giving high-dose or adjuvanted influenza vaccination is **conditionally** recommended over giving regular-dose influenza vaccination.	PICO 9. Very low (indirect evidence only) ≠	PICO 9. In patients with RMD age ≥65 years, is high-dose influenza vaccine more effective than seasonal regular-dose influenza vaccine?	728
	PICO 10. Very low (indirect evidence only) ≠	PICO 10. In patients with RMD age ≥65 years, is adjuvanted influenza vaccine more effective than seasonal regular-dose influenza vaccine?	728
	PICO 11. Moderate	PICO 11. In patients with RMD <65 years of age, is high-dose vaccine more effective than seasonal regular-dose influenza vaccine?	728–737
	PICO 12. Very low (indirect evidence only) ≠	PICO 12. In patients with RMD <65 years of age, is adjuvanted influenza vaccine more effective than seasonal regular-dose influenza vaccine?	737
Pneumococcal vaccination			
For patients with RMD age <65 years who are taking immunosuppressive medication, pneumococcal vaccination is **strongly** recommended.	PICO 20. Low	PICO 20. Should patients with RMD receive vaccination against pneumococcus at age <65 years?	933–952
Recombinant VZV vaccination			
For patients with RMD age >18 years who are taking immunosuppressive medication, administering the recombinant VZV vaccine is **strongly** recommended.	PICO 21. Very low (indirect evidence only) ≠	PICO 21. Should patients with RMD receive VZV vaccination at age <50 years?	952
HPV vaccination			
For patients with RMD age >26 and <45 years who are taking immunosuppressive medication and are not previously vaccinated, vaccination against HPV is **conditionally** recommended.	PICO 19. Very low	PICO 19. Should patients with RMD be vaccinated against HPV at age >26 years?	931–933
Whether to hold immunosuppressive medication at the time of non–live attenuated vaccination to maximize vaccine immunogenicity, although holding medications could be associated with disease flare			
For patients with RMD, *holding* methotrexate for 2 weeks after influenza vaccination is **conditionally** recommended, assuming disease activity allows.	PICO 3. Very low for most comparisons, moderate for a few	PICO 3. In patients with [RMD disease X], what is the effect of [drug Y/drug class] on immunization responses to [vaccine Z, vaccine type] in comparison with [general population, or drug Y]?	7–550
	PICO 15. TNFi: low; tocilizumab: very low; secukinumab: very low; tofacitinib: moderate;	PICO 15. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking drug Y as compared to those not taking drug Y at the time of vaccination?	754–898

Recommendations	Level of evidence†	PICO	Evidence table page numbers
	glucocorticoids: very low; abatacept: very low		
	PICO 16. MTX: moderate; tofacitinib: low; other medications: indirect evidence only	PICO 16. Should patients with RMD taking drug Y hold their drug Y for a period of time prior to or after receiving (not live attenuated) vaccines?	898–927
For patients with RMD, continuing immunosuppressive medications other than methotrexate around the time of influenza vaccination is **conditionally** recommended.	PICO 3. Very low for most comparisons, moderate for a few	PICO 3. In patients with [RMD disease X], what is the effect of [drug Y/drug class] on immunization responses to [vaccine Z, vaccine type] in comparison with [general population, or drug Y]?	7–550
	PICO 15. TNFi: low; tocilizumab: very low; secukinumab: very low; tofacitinib: moderate; glucocorticoids: very low; abatacept: very low	PICO 15. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking drug Y as compared to those not taking drug Y at the time of vaccination?	754–898
	PICO 16. MTX: moderate; tofacitinib: low; other medications: indirect evidence only	PICO 16. Should patients with RMD taking drug Y hold their drug Y for a period of time prior to or after receiving (not live attenuated) vaccines?	898–927
For patients with RMD, continuing immunosuppressive medications around the time of other (non-influenza) non–live attenuated vaccinations is **conditionally** recommended.	PICO 3. Very low for most comparisons, moderate for a few	PICO 3. In patients with [RMD disease X], what is the effect of [drug Y/drug class] on immunization responses to [vaccine Z, vaccine type] in comparison with [general population, or drug Y]?	7–550
	PICO 16. MTX: moderate; tofacitinib: low; other medications: indirect evidence only	PICO 16. Should patients with RMD taking drug Y hold their drug Y for a period of time prior to or after receiving (not live attenuated) vaccines?	898–927
Timing vaccinations in patients receiving rituximab to maximize vaccine efficacy			
For patients with RMD receiving rituximab, administering influenza vaccination on schedule is **conditionally** recommended rather than deferring vaccination until the next rituximab administration is due. For patients with RMD receiving rituximab, *deferring* non–live attenuated vaccinations, other than influenza vaccination, until the next rituximab administration is due, and *delaying* rituximab for 2 weeks after vaccination, is **conditionally** recommended.	PICO 17. Low	PICO 17. Should patients with RMD who are taking rituximab time non–live attenuated vaccine administration relative to the next dose of medication?	927–930
Whether to administer non–live attenuated vaccinations to patients receiving glucocorticoids or defer vaccination to a later time point to maximize vaccine immunogenicity			
For patients with RMD who are taking the equivalent of prednisone ≤10 mg daily, administering any non–live attenuated vaccinations is **strongly** recommended.	PICO 4. Low for pneumococcal vaccines, very low for other vaccines	PICO 4. In patients with RMD, does the immunogenicity or efficacy of vaccine Z differ in patients taking high-dose teroids as compared to those taking lower doses of steroids or those not taking steroids?	551–579

Recommendations	Level of evidence[†]	PICO	Evidence table page numbers
	PICO 14. Very low	PICO 14. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	739–754
For patients with RMD who are taking the equivalent of prednisone >10 mg daily but <20 mg daily, administering any non–live attenuated vaccinations is **conditionally** recommended.	PICO 4. Low for pneumococcal vaccines, very low for other vaccines	PICO 4. In patients with RMD, does the immunogenicity or efficacy of vaccine Z differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	551–579
	PICO 14. Very low	PICO 14. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	739–754
For patients with RMD taking the equivalent of prednisone ≥20 mg daily, administering influenza vaccination is **conditionally** recommended.	PICO 14. Very low	PICO 14. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	739–754
For patients with RMD who are taking the equivalent of prednisone ≥20 mg daily, *deferring* non–live attenuated vaccinations, other than the influenza vaccine, until glucocorticoids are tapered to the equivalent of prednisone <20 mg daily is **conditionally** recommended.	PICO 4. Low for pneumococcal vaccines, very low for other vaccines	PICO 4. In patients with RMD, does the immunogenicity or efficacy of vaccine Z differ in patients taking high-dose steroids as compared to those taking lower doses of steroids or those not taking steroids?	551–579
Whether to defer vaccination in patients with high disease activity to maximize vaccine immunogenicity and/or avoid worsening disease activity			
For patients with RMD, giving non–live attenuated vaccinations is **conditionally** recommended regardless of patients' disease activity.	PICO 13. Very low	PICO 13. In patients with RMD, does the immunogenicity or efficacy of influenza vaccine differ in patients who have moderate to severely active underlying disease as compared to those in low disease activity or remission?	737–739
	PICO 18. Very low	PICO 18. Should moderately to severely ill patients with RMD with disease X defer vaccination (not live attenuated) until the disease is better controlled?	930–931
Managing immunosuppressive therapy at the time of live attenuated vaccination to avoid vaccine-associated illness			
For patients with RMD who are taking immunosuppressive medication, *deferring* live attenuated vaccines is **conditionally** recommended.	PICO 23. Very low	PICO 23. Should patients with RMD taking drug Y receive live attenuated vaccines?	952–960
For patients with RMD, *holding* immunosuppressive medication for an appropriate period before and 4 weeks after live attenuated virus vaccination is **conditionally** recommended.	PICO 24. Very low	PICO 24. Should patients with RMD taking drug Y hold the drug for a period of time prior to or after receiving live attenuated vaccines?	960–964
When to administer rotavirus vaccine to infants with second- and/or third-trimester antenatal exposure to biologic DMARDs in utero			
For neonates/infants with second- and/or third-trimester antenatal exposure to TNFi, giving live attenuated rotavirus vaccine within the first 6 months of life is **conditionally** recommended.	PICO 25. Very low	PICO 25. Should neonates/infants with second- and third-trimester antenatal exposure to TNFi or rituximab receive live attenuated rotavirus vaccine in their first 6 months of life?	964–966

Recommendations	Level of evidence[†]	PICO	Evidence table page numbers
For neonates/infants with second- and/or third-trimester antenatal exposure to rituximab, *delaying* live attenuated rotavirus vaccine until >6 months of age is **conditionally** recommended.	PICO 25. Very low	PICO 25. Should neonates/infants with second- and third-trimester antenatal exposure to TNFi or rituximab receive live attenuated rotavirus vaccine in their first 6 months of life?	964–966
Whether to give multiple vaccinations to patients with RMD on the same day			
For patients with RMD, giving multiple vaccinations on the same day rather than giving each individual vaccination on a different day is **conditionally** recommended.	PICO 22. Very low (indirect evidence only)[≠]	PICO 22. Should patients with RMD receive standardized regimens of vaccine combinations?	952

= Strong recommendation.

= Conditional recommendation.

[*] PICO = population, intervention, comparator, outcomes; RMD = rheumatic and musculoskeletal disease; VZV = varicella-zoster virus; HPV = human papillomavirus; MTX = methotrexate; TNFi = tumor necrosis factor inhibitors; DMARDs = disease-modifying antirheumatic drugs.

[†] The terms "moderate", "low", and "very low" are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) definitions for quality of evidence. Moderate quality means that "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate." Low quality means that "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate." Very low quality means that "we are very uncertain about the estimate." In the systematic review for this guideline, a judgment of moderate quality required at least some evidence from randomized controlled trials, and a judgment of low quality required at least some evidence from well-designed observational studies with appropriate comparator groups.

[≠] Indirect evidence indicates that there is evidence from other populations with RMD or other health conditions, or evidence that does not fully address the comparison specified in a PICO question.

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