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The Italian Society of Rheumatology clinical practice guidelines for the management of vaccines in adult patients with rheumatic diseases

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Abstract

Objective. Rheumatic and musculoskeletal diseases (RMDs) represent a significant public health challenge in Italy. RMDs are often chronic and lead to increased morbidity and mortality, partly due to an increased risk of infections. Patients with RMDs and those on immunosuppressive therapy show a higher susceptibility to vaccine-preventable diseases and to serious complications in case of infection. Therefore, vaccination is a crucial tool to reduce these risks. This guideline was developed by the Italian Society of Rheumatology and aimed to provide updated national recommendations for clinical practice on vaccinations in adult patients with RMDs.
Methods. The GRADE ADOLOPMENT approach to combine adoption, adaptation, or de novo development of recommendations was used, and the 2022 American College of Rheumatology (ACR) guideline on vaccinations in RMDs was used as reference. The development process included an updated systematic review of the available evidence and an assessment of the ACR guidelines and their adaptability to the Italian context, followed by a discussion with experts in rheumatology and public health and representatives of healthcare professionals and patients.
Results. A set of recommendations was developed, and special attention was given to the current vaccination schedule and to the adjustment of anti-rheumatic drugs to optimize the response to vaccines.
Conclusions. This guideline is a step forward in enhancing management and clinical practice for RMD patients in Italy and provides specific and evidence-based indications for infection prevention through vaccination. Their use is intended to promote health and alleviate the burden of morbidity and mortality in this vulnerable population.

Key words: clinical practice guideline, recommendations, rheumatic diseases, vaccines, vaccination.

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Introduction

Rheumatic musculoskeletal diseases (RMDs) pose a significant challenge for a large portion of the Italian population, affecting both adults and children (1). These conditions, including autoimmune, inflammatory, and chronic-degenerative diseases, are widespread in our country and are associated not only with disability but also with increased mortality. Globally, they account for the loss of over 100 million years of life annually (years of life lost) (2). A significant portion of this increased mortality is attributable to a higher risk of infections (3).

The treatment of these diseases often requires prolonged use of immunosuppressive drugs, exposing patients to a higher risk of developing common or opportunistic infections, including those preventable by vaccination (4, 5). Moreover, such therapies can influence the immune response to vaccines, making the optimization of vaccination strategies crucial for this vulnerable population.

Vaccines play a fundamental role in promoting public health and preventing numerous infectious diseases. The use of vaccines to control viral and bacterial diseases has been a well-established practice worldwide for over a century. In Italy, the National Vaccination Prevention Plan (PNPV) sets guidelines for the vaccination schedule for both children and adults, with the latest version, the PNPV 2023-2025 (6). Nonetheless, there are vaccines that may not have been included in previous programs or that require special considerations, such as those for travelers or newly developed vaccines like those against SARS-CoV-2.

Currently, Italy lacks a unified document providing shared national guidelines on vaccinations in patients with RMDs. This absence generates a significant gap in clinical practice, considering that patients with RMDs and those undergoing immunosuppressive therapy are more susceptible to vaccine-preventable diseases and have a higher risk of developing severe complications if infected (7, 8). Although vaccines have demonstrated efficacy in preventing infections and associated complications even in these patients, the lack of specific guidelines makes it difficult to implement optimal vaccination strategies.

The most recent international guidelines, such as those published by the American College of Rheumatology (ACR) in 2023 (9, 10), offer detailed recommendations on vaccinations for this population. However, adapting these guidelines to the Italian context is essential to consider the country's specific regulatory, epidemiological, and clinical characteristics.

In response to these needs, the Italian Society of Rheumatology (SIR) has decided to develop new national clinical practice guidelines on vaccinations in patients with RMDs, in accordance with the requirements of the National Guidelines System (SNLG) of the Italian National Institute of Health (ISS). Thus, the primary objective is to provide updated, evidence-based recommendations to improve the management of vaccinations in this population, in harmony with the current PNPV and the related national vaccination schedule.

The guidelines will focus on adult patients (≥18 years) with inflammatory and immuno-mediated RMDs, including those undergoing treatment with immunosuppressive or immunomodulatory drugs. They will cover vaccinations with vaccines currently authorized in Italy, taking into account the different types of vaccines available, such as protein-based, polysaccharide, conjugated, and live attenuated vaccines.

This guideline aims to provide practical and updated recommendations, promoting effective vaccination strategies that can reduce the morbidity and mortality associated with preventable infections. The final document, including the recommendations, was endorsed by the ISS and published on the SNLG on 12th June 2024 (11).

Need for Italian guidance

Up to now, in Italy, there has been no single document with the value of a national guideline on vaccinations in patients affected by RMDs. In 2020, SIR published recommendations for vaccination against influenza and pneumococcus in patients with autoimmune rheumatic diseases (12), but comprehensive SIR guidelines on vaccinations in rheumatology patients were lacking.

Objective

These guidelines aim to provide up-to-date and evidence-based recommendations regarding the management of vaccination in patients affected by RMDs in Italy in compliance with the requirements of the ISS SNLG and in harmony with the current PNPV and the related National Vaccination Calendar.

Target patient population

Adult patients (age ≥18 years) diagnosed with RMDs, including those undergoing treatment with immunosuppressive or immunomodulatory drugs.

Audience

Physicians (specialists in rheumatology, internal medicine, clinical immunology and allergology, hygiene and public health, infectious diseases, general practitioners) and all health professionals involved in the management of patients with rheumatic disease in primary, secondary and tertiary care at both community and hospital levels. Patients, policymakers and those responsible for the organization of care on vaccinations in patients with rheumatic diseases within the Italian National Health System.

What is covered

This guideline addressed the administration of vaccines with current authorization for use in Italy in patients with RMD with and without treatment with immunosuppressive or immunomodulatory drugs, including glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs and biological therapies commercially available in Italy.

Specifically, for the purposes of developing the recommendations, the following vaccines were included: Protein/Subunit/Recombinant/Inactivated agent (Seasonal influenza inactivated, injectable, standard dose, high dose, adjuvanted; Tetanus/Diphtheria/Acellular pertussis, Tetanus toxoid, Diphtheria and Acellular pertussis: T, dT, dTpa; Hepatitis B; Human Papilloma Virus - HPV); Hepatitis A; Herpes Zoster - adjuvanted recombinant vaccine - RZV; Meningococcus B - MenB; inactivated polio - IPV), polysaccharide (Pneumococcus - PPSV23; typhoid - Vi-PS, injectable), conjugates (Pneumococcus - PCV13, PCV15, PCV20; Meningococcus ACWY conjugated - MenACWY; *H. influenzae* b - Hib), live attenuated vaccines (Measles, Mumps, Rubella - MMR; Yellow fever - YE; Zoster - live attenuated vaccine - ZVL; Varicella; influenza live attenuated; Typhoid - live attenuated, oral Ty21a).

Vaccines against the coronavirus SARS-CoV-2 and the associated disease COVID-19 were considered. However, the rapid and constant evolution of scientific literature and the need to provide recommendations in a short time on this clinically significant and timely area has prompted the decision to proceed with a non-systematic review of the scientific evidence on the subject and to

implement consensus mechanisms among experts for the development of recommendations with the value of statements for good clinical practice.

Areas that are not covered

Not included are pediatric patients (<18 years), vaccines not approved for use in Italy, and immunotherapy (*e.g.*, Phi-X174 bacteriophage, anti-KLH vaccine - keyhole limpet hemocyanin).

Materials and Methods

Approach to guideline development

The Grading of Recommendations Assessment, Development and Evaluation (GRADE)-ADOLOPMENT methodology (13) was used to identify existing and relevant guidelines on the topic in accordance with the methodological manual for the production of clinical practice guidelines (version 1.3.3, March 2023) (14) of the National Center for Clinical Excellence, Quality and Safety of Care of the Italian National Institute of Health (CNEC). The GRADE-ADOLOPMENT approach to guideline production combines adoption, adaptation, and, as needed, de novo development of recommendations, and the transparency is ensured by a detailed and full reporting of the process as described in the following paragraphs. The SIR Board of Directors, in the role of Technical Scientific Committee, appointed the project Steering Committee (21st October 2022) for the assembly of the panel and approved the choice of the guideline topic, the activity plan, and the use of resources. For the application of the GRADE-ADOLOPMENT methodology, the guidelines on vaccinations in RMDs issued by the ACR were identified as a reference (9). The project was approved by the Steering Committee and the final protocol for the development of the guidelines was approved by the panel (version 1.1, April 16, 2023).

Assembly of the working groups

On behalf of the Technical Scientific Committee, the developer (N.U.) and the Evidence Review Team (R.P., G.A., G.C., G.L., D.R.) of the SIR Study Center worked in collaboration with a multidisciplinary panel of clinicians with specialist experience in rheumatology, allergology and clinical immunology, internal medicine, hygiene and public health, medical microbiology and virology (Steering Committee: A.D. - Chair, M.M., F.C., C. P.; panel members: M.P., S.F., R.C., A.B., C.S., S.B., S.G., G.S., L.S., G.G), a nurse (K.E.A.) and a representative (S.T.) of the National Association of Rheumatic Patients (ANMAR) through e-mail discussions, web-meetings, and participation in online surveys (*via* REDcap®). The threshold of 75% of the participants was stated as a requisite to consider the discussions, as well as the ratings, to be valid for the purpose of developing the final recommendations.

Stakeholder involvement

A multidisciplinary, multiprofessional and nationwide group of clinicians, health professionals, on behalf of the Italian Forum of Healthcare Professionals in Rheumatology (ForRheuma) and patient representatives from the Voluntary Organizations (ODV) ANMAR, Gruppo LES Italiano, AILS, and GILS were invited to evaluate and vote on the outcomes and the text of these recommendations. These recommendations were developed without any contribution or collaboration with any pharmaceutical company or industry.

Defining the scope

On the basis of a set of key clinical questions structured according to the PICO (population, intervention, comparator, outcome) framework from the reference guideline (9), the disease outcomes were assessed by the panel (3rd to 15th May, 2023) and by the stakeholders (13th to 27th July, 2023) and the outcomes whose evaluation was "critical" or "important but not critical" were used to guide the systematic search for scientific evidence.

Search strategy, data extraction and synthesis into the evidence profile

The literature search was based on the keywords and strings adopted from the reference recommendations and in accordance with the outcome voting. The Evidence Review Team assessed the quality of the reference ACR recommendations using the Appraisal of Guidelines Research and Evaluation (AGREE) II online tool and 3 assessors (N.U., R.P., G.A.) assigned a score and a global judgment for each guideline. A first update of the scientific evidence was performed by conducting a systematic review from the end date of the reference guideline search (31st January, 2022) to 12th April, 2023 and a second update to 30th June, 2023. The following databases were queried: Medline (*via* Ovid), Embase (*via* Ovid), and Cochrane Library (*via* Cochrane Central). The Evidence Review Team carried out the selection of studies and data extraction (at least two members independently). For the scientific literature search, the following inclusion criteria were applied: English or Italian or other language if translation was available; response to clinical questions; all study designs (experimental and observational clinical studies, clinical cases if with a number of subjects greater than or equal to 5). Publications as recommendations or guidelines or consensus, clinical cases with a number of subjects less than 5, in languages for which it was not possible to obtain translation and with no response to clinical questions were excluded. The flow of study selection is shown in Figure 1. The results of data extraction updated to the reference guideline were summarized and reported in synoptic tables (evidence profile) divided by PICO. Given the rapid and constant evolution of scientific literature and the need to quickly provide recommendations on significant clinical areas, as regards vaccines against SARS-CoV-2 and COVID-19, it was decided to proceed from the reference recommendations (10) through a non-systematic review of the scientific evidence. Studies were identified and data were extracted if deemed relevant for the development of good practice statements on COVID-19 in compliance with the GRADE criteria (15).

Critical appraisal of quality

The quality of the evidence retrieved by the systematic search was assessed by the Evidence Review Team in accordance with the GRADE method through the analysis of the following domains: limitations (Quantification of the Risk of Bias), inconsistency, indirectness, imprecision and publication bias (by visualization of funnel plots and Egger test). The risk of bias was assessed through the following tools: Risk of Bias in Non-randomised Study of Interventions (ROBINS)-I (16), Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (17) for treatment. The assessment of the quality of the evidence also took into account the 3-grade criteria for the possible upgrading of observational studies (effect size, dose-response relationship and confounding factors). Finally, an overall quality rating was assigned to the evidence using the terms "high", "moderate", "low" and "very low" based on the expected impact on the confidence placed in the estimate of effect (Table 1).

From the evidence profile to the evidence-to-decision framework and the development of the recommendations

The results of the Evidence Profile updated to the reference guideline and the quality assessment were reported within the evidence-to-decision (EtD) framework and the recommendations were discussed by the panel *via* web-meeting (4th and 5th July, 2023, and 29th November, 2023). Therefore, given the available scientific evidence and the scarcity and heterogeneity of the studies, a judgment was made on the strength of the recommendations, assessed as strong or conditional in line with the perspectives of patients, clinicians and policymakers (Table 1). The Panel's considerations on the strength of the recommendations, on the risks and benefits and on the applicability were reported in the EtD tables on the basis of the updated evidence.

Finally, regarding vaccines against the SARS-CoV-2 and the COVID-19, the recommendations include the indications of Good Practice Statements which were defined on the basis of a consensus mechanism among the panel experts and the criteria of clarity and feasibility of the indications, great relevance for clinical practice, particularly favorable expected impact on health resulting from their application, time and resource limits for research and the synthesis of the available scientific evidence used for their development (15).

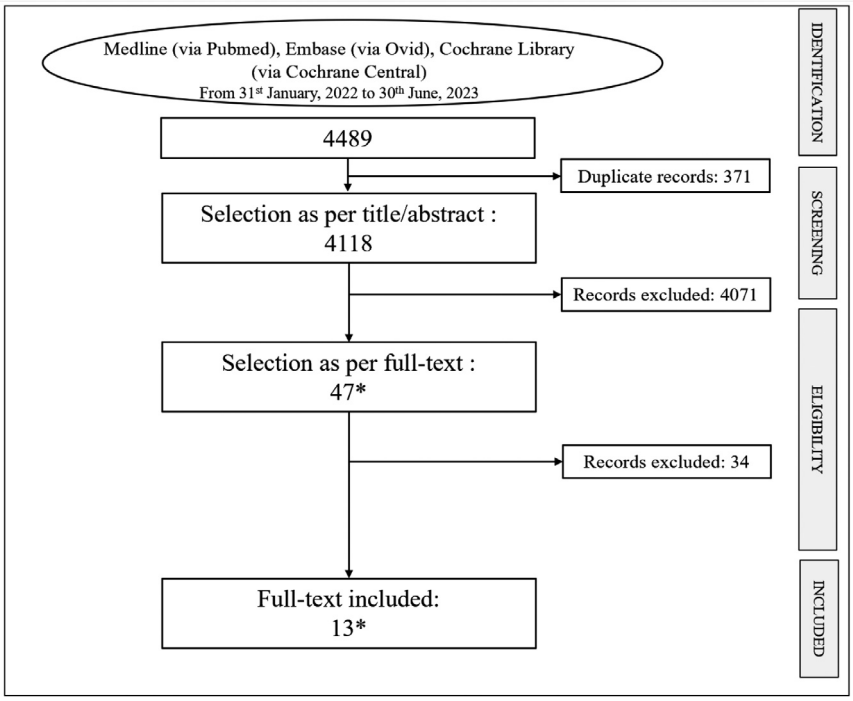

Figure 1. Flow of the systematic research of the scientific literature. *Studies involving vaccines against the coronavirus SARS-CoV-2 and the associated disease COVID-19 were not included in the systematic search.

Table 1. Guidance for the appraisal of the quality of evidence and strength of the recommendations in accordance with the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach.

Quality of evidence	Expected impact on confidence of the estimate of the effect		
High	"Further research is very unlikely to change our confidence in the estimate of effect"		
Moderate	"Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"		
Low	"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	"Any estimate of effect is very uncertain"		
Strength of the recommendation	**Patients**	**Clinicians**	**Policy makers**
Strong	Most people in this situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be adapted as a policy in most situations.
Conditional	The majority of people in this situation would want the recommended course of action, but many would not.	Be prepared to help patients to make a decision that is consistent with their own values.	There is a need for substantial debate and involvement of stakeholders.

The AGREE checklist for the publication of the guidelines was used as a guideline for the final version of these recommendations (18).

Approval of the recommendations, stakeholders' consultations and external revision

The panel members evaluated the draft recommendations *via* online surveys (1st round: from 25th August to 19th September, 2023; 2nd round: from 9th to 20th December 2023; 14/16 and 16/16 complete responses, response rate 87.5% and 100%, respectively) and a score from 1 (worst) to 9 (best) was assigned to each recommendation. An average score higher than 7 was defined *a priori* for the purposes of validation and approval of the guideline for use in clinical practice.

Stakeholders were consulted to comment and vote (same score from 1 to 9) on the preliminary version of the recommendations *via* an online survey (27th December 2023 to 10th January 2024, *via* REDcap®). Comments were taken into account in the development of the final version of the recommendations.

An external review was conducted by consulting two experts (one rheumatologist, one specialist in hygiene and public health) who were not involved during the development process of the guideline. The consultation took place *via* an online survey (11th to 24th April 2024, *via* REDcap®) and each external reviewer was asked to assign a score from 1 (completely disagree) to 9 (completely agree) and to provide any comments for each recommendation. In addition, an assessment of the overall quality of the guideline was requested using the AGREE II tool.

Recommendations

The current Italian vaccination schedule is regulated by the PNPV 2023-2025 document, which defines the national recommendations for vaccinations for children and adults. Starting from these, this guideline document incorporates and integrates the recommendations regarding vaccines for adults with the peculiarities of RMDs and with the specificities of the related immunosuppressive treatments. The panel identified the following general principles regarding vaccinations, which should be reported before the statements of the recommendations (Table 2). First, it is important to administer any necessary vaccinations before starting immunosuppressive therapy in patients with RMD, if possible. Secondly, for family members, cohabitants and other relatives who have frequent contact with RMD patients undergoing immunosuppressive therapy, some vaccinations are recommended in order to facilitate the cocooning effect and to protect the patient with RMD.

The good clinical statements on vaccines against SARS-CoV-2 and COVID-19 are reported at the end of the guideline (Table 3).

The results of the systematic review search, the synthesis of the evidence in Evidence Profile tables and the EtD tables, along with the quality appraisal, and the results of surveys by panel members and stakeholders, were reported in the appendices of the original document (11).

Recommendations on inactivated vaccines (COVID-19 excluded)

The following vaccines were considered: seasonal influenza (standard dose, high dose, with adjuvant), Pneumococcus (polysaccharide and conjugate vaccines), HPV, Hib, Hepatitis A, Hepatitis B, IPV, MenB, MenACWY conjugate, T/Td/Tdap, Vi-PS, RZV. The pneumococcal vaccines PCV15 and PCV20 were not included in the systematic search, but considered together with PCV13 and PPSV23.

Influenza vaccination is strongly recommended for patients with rheumatic musculoskeletal diseases aged ≥65 years and for patients with rheumatic musculoskeletal diseases aged ≥18 years and <65 years who are receiving, or are planning to start, an immunosuppressive therapy

The expected clinical benefit and the risk/benefit ratio of the administration of influenza vaccination are such that the indication for the recommendation has been defined as strong. In line with the regulation of the Italian Ministry of Health on influenza vaccination (21/04/2023, n. 12781), the inactivated influenza vaccines currently authorized for use in Italy are quadrivalent vaccines (VIQ) that contain 2 type A viruses (H1N1 and H3N2) and 2 type B viruses. In subjects aged 65 years and older, the use of enhanced vaccines is recommended (VIQa, adjuvanted quadrivalent inactivated vaccine; VIQhd, high-dose quadrivalent inactivated vaccine). The cell-cultured inactivated quadrivalent vaccine can be used from 2 years of age; the quadrivalent inactivated recombinant DNA vaccine can be used from 18 years of age; VIQa can be used from 50 years of age; VIQhd can be used from 60 years of age. This recommendation differs from what is stated in the ACR reference guidelines, where the high-dose or adjuvanted influenza vaccination was conditionally recommended over regular-dose influenza vaccination.

Pneumococcal vaccination is strongly recommended for patients with rheumatic musculoskeletal diseases who are receiving immunosuppressive therapy

The quality of evidence is low due to the number and characteristics of the studies available on populations with RMDs. However, the expected clinical benefit and the risk/benefit ratio of the administration of the pneumococcal vaccination are such that the indication for the recommendation has been defined as strong. Currently, two types of pneumococcal vaccines are available: the polysaccharide vaccine (PPSV-23) and the conjugated vaccine (PCV). For PCV in adults, vaccines with different valences are available (PCV-13, PCV-15, PCV-20). The vaccination calendar included in the PNPV 2023-2025 for subjects at risk due to pathological conditions provides for the priority offer of vaccination with the conjugated vaccine. The offer should be integrated with a sequential vaccination schedule (PCV + PPSV) depending on the type of PCV vaccine used. For the sequential schedule, PCV administration must precede PPSV administration (PCV dose followed at least 8 weeks later by a PPSV dose).

Adjuvanted recombinant Zoster vaccine is strongly recommended for patients with rheumatic musculoskeletal diseases and age ≥18 years who are receiving immunosuppressive therapy

The quality of evidence is very low due to the number and characteristics of the studies available on populations with RMDs. However, the expected clinical benefit and the risk/benefit ratio of the administration of the Zoster vaccination are such that the indication for the recommendation has been defined as strong. The vaccination schedule included in the PNPV 2023-2025 for subjects with immunodeficiency or intended for immunosuppressive therapy recommends the use of RZV (two-dose schedule).

Vaccination against Human Papilloma Virus is conditionally recommended for patients with rheumatic musculoskeletal diseases who are taking immunosuppressive therapy and have not been previously vaccinated

The PNPV 2023-2025 recommends HPV vaccination for women who have been treated for cervical intraepithelial neoplasia (CIN)2+ or higher- grade lesions. Vaccination may be administered before

Table 2. Recommendations on vaccines in patients with rheumatic diseases.

	Recommendation	Quality of evidence	Strength
1.0 Inactivated vaccines			
1.1	Influenza vaccination is strongly recommended for patients with RMD aged ≥65 years and for patients with RMD aged ≥18 years and <65 years who are receiving, or are planning to start, an immunosuppressive therapy.	Very low	Strong
1.2	Pneumococcal vaccination is strongly recommended for patients with RMD who are receiving immunosuppressive therapy.	Low	Strong
1.3	Adjuvanted recombinant Zoster vaccine is strongly recommended for patients with RMD and age ≥18 years who are receiving immunosuppressive therapy.	Very low	Strong
1.4	Vaccination against human papilloma virus is conditionally recommended for patients with RMD who are taking immunosuppressive therapy and have not been previously vaccinated.	Very low	Conditional
2.0 Immunosuppressive drugs when the administration of inactivated vaccines is planned			
2.1	In patients with RMD, where possible in relation to disease activity, the discontinuation of methotrexate 1 to 2 weeks after influenza vaccination is conditionally recommended.	Moderate	Conditional
2.2	In patients with RMD, the continuation of the immunosuppressive therapy during influenza vaccination is conditionally recommended.	Very low (low for tofacitinib)	Conditional
2.3	In patients with RMD, the continuation of the immunosuppressive and/or immunomodulatory therapy is conditionally recommended when inactivated vaccines are administered (influenza excluded).	Very low (moderate for methotrexate, low for tofacitinib)	Conditional
2.4	In patients aged ≥18 years with RMD and undergoing treatment with rituximab, the administration of influenza vaccination at the scheduled time is conditionally recommended rather than deferring vaccination until the next treatment with rituximab is scheduled.	Low	Conditional
2.5	In patients with rheumatologic disease treated with rituximab, deferring the administration of inactivated vaccines (excluding influenza) until the next rituximab treatment is scheduled and deferring rituximab treatment for 2 weeks after vaccination are conditionally recommended.	Low	Conditional
2.6	In patients with RMD who are receiving glucocorticoid therapy at a prednisone equivalent dose ≤10 mg per day, the administration of inactivated vaccines is strongly recommended.	Very low (low for pneumococcal vaccination)	Strong
2.7	In patients with RMD who are taking glucocorticoids at a prednisone equivalent dose >10 mg per day but <20 mg per day, the administration of inactivated vaccines is conditionally recommended.	Very low (low for pneumococcal vaccination)	Conditional
2.8	In patients with RMD who are taking glucocorticoids at a prednisone equivalent dose ≥20 mg per day, the administration of influenza vaccination is conditionally recommended.	Very low	Conditional
2.9	In patients with RMD who are taking glucocorticoids at a prednisone equivalent dose ≥20 mg per day, deferring administration of inactivated vaccines (excluding influenza) until the therapy has been reduced to a prednisone equivalent dose <20 mg per day is conditionally recommended.	Very low (low for pneumococcal vaccination)	Conditional
2.10	In patients with RMD, the administration of inactivated vaccines is suggested regardless of the patient's disease activity.	Very low (low for pneumococcal vaccination)	Conditional
3.0 Immunosuppressive drugs and the administration of live attenuated vaccines			
3.1	In patients with RMD where the discontinuation of immunosuppressive therapy is not possible, deferring the administration of live attenuated vaccines is strongly recommended.	Very low	Strong
3.2	In patients with RMD where the discontinuation of immunosuppressive therapy is possible, the discontinuation of the treatment for a timing related to the drug before and 4 weeks after the administration of live attenuated vaccines is strongly recommended.	Very low	Strong
4.0 Multiple administrations of inactivated vaccines			
4.1	In patients with RMD, co-administration of multiple vaccines on the same day is conditionally recommended rather than deferring the administration on the following days.	Very low	Conditional

RMD, Rheumatic and musculoskeletal diseases.

treatment or subsequently, up to a maximum of 3 years after treatment itself. For subjects aged 15 years or older at the time of the first administration, a 3-dose schedule is planned. In line with the PNPV, this recommendation does not specify age limits, differently from what is explicitly stated in the ACR reference guidelines, where the administration between 26 years and 45 years is conditionally recommended.

Recommendations on immunosuppressive drugs when the administration of inactivated vaccines is planned

The following drugs were considered: methotrexate, azathioprine, leflunomide, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide, tumor necrosis factor inhibitors, anti-interleukin (IL)-6 receptor, IL-17 inhibitors, anti-IL-1 receptor, IL-12/23 inhibitors, IL-23 inhibitors, B-cell activating factor (BAFF)/B Lymphocyte Stimulator (BLyS) inhibitor (belimumab), Janus Kinase inhibitors, CTLA4 fusion molecule (abatacept), anti-CD20 (rituximab), anti-IFN type 1 receptor (anifrolumab).

In patients with rheumatic musculoskeletal diseases, where possible in relation to disease activity, the discontinuation of methotrexate 1 to 2 weeks after influenza vaccination is conditionally recommended

This recommendation was modified after the update of the scientific evidence. A randomized controlled trial in 178 patients with rheumatoid arthritis showed the non-inferiority of the discontinuation of methotrexate for 1 *vs.* 2 weeks in terms of efficacy in seroconversion (19). Safety for any adverse event was comparable, while the findings on potential exacerbation of disease activity were inconsistent. The mean disease activity score (DAS-28) changes from baseline and after 4 weeks were comparable between the 1-week hold and 2-week hold (p=0.365), but the proportions of disease flare defined on DAS-28 increase cut-offs were 4.5% of 90 patients in the 1-week hold group and 12.9% of 88 patients in the 2-week hold group (p=0.05). The need for rescue medications was comparable between the two groups (19).

In patients with rheumatic musculoskeletal diseases, the continuation of the immunosuppressive therapy during influenza vaccination is conditionally recommended

In patients with rheumatic musculoskeletal diseases, the continuation of the immunosuppressive and/or immunomodulatory therapy is conditionally recommended when inactivated vaccines are administered (influenza excluded)

These recommendations do not include treatments with methotrexate and rituximab, which are considered in recommendations 2.1, 2.4, and 2.5. The implementation of these recommendations is conditioned both by disease activity and the specificity of the RMD, as well as by the clinical history of the patient with whom the choice should be shared.

In patients aged ≥18 years with rheumatic musculoskeletal diseases and undergoing treatment with rituximab, the administration of influenza vaccination at the scheduled time is conditionally recommended rather than deferring vaccination until the next treatment with rituximab is scheduled

In patients with rheumatologic disease treated with rituximab, deferring the administration of inactivated vaccines (excluding influenza) until the next rituximab treatment is scheduled and deferring rituximab treatment for 2 weeks after vaccination are conditionally recommended

The deferral of rituximab administration is conditioned by disease activity and the choice to defer treatment should be taken into consideration if the activity of the RMD allows it according to the clinical judgment.

In patients with rheumatic musculoskeletal diseases who are receiving glucocorticoid therapy at a prednisone equivalent dose ≤10 mg per day, the administration of inactivated vaccines is strongly recommended

Despite the very low quality of the recommendation resulting not only from the characteristics of the studies but also from the indirect evidence, the expected clinical benefit and the risk/benefit ratio of the administration of inactivated vaccines are expected to be so high that the indication for the recommendation has been defined as strong.

In patients with rheumatic musculoskeletal diseases who are taking glucocorticoids at a prednisone equivalent dose >10 mg per day but <20 mg per day, the administration of inactivated vaccines is conditionally recommended

In patients with rheumatic musculoskeletal diseases who are taking glucocorticoids at a prednisone equivalent dose ≥20 mg per day, the administration of influenza vaccination is conditionally recommended

In patients with rheumatic musculoskeletal diseases who are taking glucocorticoids at a prednisone equivalent dose ≥20 mg per day, deferring administration of inactivated vaccines (excluding influenza) until the therapy has been reduced to a prednisone equivalent dose <20 mg per day is conditionally recommended

These recommendations are all in favor of vaccination intervention and, in particular, of influenza vaccination, which is recommended in line with the regulation of the Minister of Health "Prevention and control of influenza: recommendations for the 2023-2024 season" (21/04/2023, n. 12781). These recommendations confirm the favorable direction for the intervention and its importance and, at the same time, they reflect the paucity of the body of evidence supporting them. These recommendations were approved after the minimum overall score required for approval was exceeded during the voting of the panel members. However, the discussion of these recommendations, in particular 3.2.8, was conflicting, particularly with reference to the strength of the recommendation and the need to maintain a distinction between the different dosages of glucocorticoids. First of all, the panel agreed on the importance of influenza vaccination and no conflicts emerged on the direction of the recommendation in favor of influenza vaccination. With regard to the divergence, it was underlined that in the regulation of the Circular of the Ministry of Health for the 2023-2024 season the condition of immunosuppression is not a contraindication, but a recommendation to the administration of influenza vaccination, except as specified regarding the live attenuated vaccine. Moreover, no mention about to the dose of glucocorticoids was made in the regulation. On the other hand, it has been highlighted that in clinical practice, glucocorticoid doses, and in particular those >20 mg per day, are frequently subject to modulation in down-titration to doses <20 mg per day and sometimes with timing compatible with the seasonality of the influenza vaccination campaign. The last reasoning was considered critical for the strength of the recommendation and its applicability. Finally, it is worth reporting that the threshold of glucocorticoid doses (10 and

20 mg per day) is drawn from the definitions used in comparative studies on the immunogenicity of the administration of inactivated vaccines and exposure to glucocorticoids in some rheumatological populations (specifically in systemic lupus erythematosus and rheumatoid arthritis).

In patients with rheumatic musculoskeletal diseases, the administration of inactivated vaccines is suggested regardless of the patient's disease activity

Recommendations on immunosuppressive drugs and the administration of live attenuated vaccines

The following vaccines were considered: MMR, Oral Typhoid, VZV, YE, ZVL.

In patients with rheumatic musculoskeletal diseases where the discontinuation of immunosuppressive therapy is not possible, deferring the administration of live attenuated vaccines is strongly recommended

In patients with rheumatic musculoskeletal diseases where the discontinuation of immunosuppressive therapy is possible, the discontinuation of the treatment for a timing related to the drug before and 4 weeks after the administration of live attenuated vaccines is strongly recommended

The strength of the recommendation was debated and the lack of complete alignment among some members of the panel was pointed out. In the face of a very low quality of the supporting evidence, the recommendation was approved by the majority of the panel members based on the need to apply the precautionary principle and specifically on the potential for harm to the patient resulting from the administration of live attenuated vaccines in a condition of immunosuppression. Furthermore, the same precautionary principle is to be considered valid in the application of the recommendation in terms of suspension of treatment, given the significant heterogeneity of the rheumatological populations involved and the diversity of the treatments to which they are subjected. In particular, the timing should be carefully chosen in line with the need of disease treatment and the half-life of the ongoing drug(s) before the vaccination.

Special considerations regarding the timing of discontinuation of immunosuppressive drugs prior to administration of live attenuated vaccines

The panel agreed that at present it is not possible to provide precise indications regarding the timing of interruption of immunosuppressive treatment before the administration of live attenuated vaccines as the topic is still controversial and the supporting scientific evidence base was deemed insufficient to develop recommendations. The ACR reference guideline reported different timing of interruption of immunosuppressive treatments (9).

Recommendations on multiple administrations of inactivated vaccines

In patients with rheumatic musculoskeletal diseases, co-administration of multiple vaccines on the same day is conditionally recommended rather than deferring the administration to the following days

Good practice statements

The good practice statements on COVID-19 vaccination are shown in Table 3.

The COVID-19 vaccination is recommended for family members, cohabitants and other relatives who have frequent contact with patients with RMDs on immunosuppressive treatment in order to facilitate the cocooning effect and protection of the patient with RMD.

The frail condition of patients with RMD undergoing pharmacological treatment conditioning secondary immunodeficiency (*e.g.*, high-dose glucocorticoid therapy, immunosuppressive drugs, biological drugs with a significant impact on the functionality of the immune system, etc.) is considered an increased risk factor for severe COVID-19 disease and a reason for recommending vaccination. The "high risk" profile for the indication of possible pre-exposure prophylaxis treatment with monoclonal antibody (*e.g.*, tixagevimab, cilgavimab) is formulated according to the clinical judgment of the clinician who knows the patient's clinical history, the specifics of the RMD, the concomitant pathologies or conditions that increased the state of fragility and the peculiarities of the ongoing immunosuppressive therapy.

Finally, the panel pointed out that patients with RMD must con-

Table 3. Good practice statements on COVID-19 vaccination for patients with rheumatic and musculoskeletal diseases on immunosuppressive treatments.

	Good practice statements	LoA Mean (SD)
1	COVID-19 vaccination should be recommended for patients with RMD regardless of disease activity and severity, with the exception of patients in life-threatening conditions (*e.g.*, admission to intensive care units for any reason).	8.5 (0.6)
2	In patients with RMD who have not yet been vaccinated, vaccines approved and available in the country should be recommended.	8.5 (0.6)
3	In patients with RMD who have received the first dose of COVID-19 vaccine, completion of the entire primary series should be recommended.	8.6 (0.6)
4	In patients with RMD who have completed the primary series of COVID-19 vaccine and who are expected to have an inadequate response to vaccination, administration of supplementary doses should be recommended.	8.3 (0.7)
5	COVID-19 vaccination (first and subsequent vaccinations, including supplemental boosters) should be recommended regardless of naturally acquired COVID-19 infection.	8.5 (0.6)
6	Laboratory tests *(e.g.*, IgM and/or IgG antibody assay against spike proteins or nucleocapsid) should not be recommended to assess the response to COVID-19 vaccination, nor to assess the need for vaccination in never-vaccinated patients.	8.6 (0.6)
7	In patients with high-risk rheumatologic disease, pre-exposure prophylaxis treatment with monoclonal antibody may be recommended.	8.5 (0.8)

RMD, Rheumatic and musculoskeletal diseases; LoA, level of agreement; SD, standard deviation. The level of agreement was measured by a score from 1 (worst) to 9 (best) and an average score higher than 7 was defined a priori for validation and approval purposes.

tinue to follow the public health indications with regard to social distancing and other measures to prevent SARS-CoV-2 infection.

Discussion and Conclusions

To date, Italy has lacked a comprehensive national guideline addressing vaccinations for patients with rheumatologic diseases. This guideline provides a set of evidence-based recommendations tailored to adult patients with rheumatologic diseases undergoing immunosuppressive therapy. These recommendations were developed in accordance with the international methodological standards and were published on the Italian SNLG in June 2024.

This guideline builds upon the prior SIR recommendations from 2020 (12), which were limited to influenza and pneumococcal vaccines, by expanding the scope to include other inactivated and live attenuated vaccines. Therefore, this new guideline fills that gap by incorporating the most recent ACR guidelines on vaccinations in patients with rheumatologic diseases (9, 10), and adapting them to the Italian healthcare context using the GRADE-ADOLOPMENT methodology (13). This method was a requirement of the ISS and was chosen due to its efficiency in resource utilization, compared to developing de novo guidelines, and allowed to incorporate high-quality evidence while addressing the unique challenges faced by Italian healthcare providers. The integration of the latest national vaccination policies (PNPV 2023-2025), the following regulations of the Ministry of Health, and the latest scientific literature has resulted in a set of recommendations that are both comprehensive and context-specific. The panel generally favored straightforward recommendations to encourage vaccination and promote adherence to the guideline. At first, the guidelines emphasize the importance of initiating vaccination prior to the commencement of immunosuppressive therapy to maximize immunogenic response. Additionally, vaccinating household members and close contacts of immunosuppressed patients is recommended to enhance the cocooning effect, thereby reducing the risk of infections within this vulnerable population. Despite these recommendations, it is critical to acknowledge that the evidence supporting the safety and immunogenicity of certain vaccines in patients on specific immunosuppressive therapies remains limited. Due to the low quality of this evidence, shared decision-making between clinicians, patients, and caregivers is crucial for the vaccination strategies presented here.

The present recommendations modify the original formulations of the 2023 ACR guidelines (9) by incorporating national contingencies, current institutional policies, and updated scientific evidence. One key modification is the guidance regarding the use of methotrexate during administration of the influenza vaccine. The updated systematic review suggests that holding methotrexate for 1 week only may enhance vaccine response without significantly increasing the risk of disease flare, though this recommendation is made cautiously due to the limited data available.

These recommendations represent a significant advancement in clinical practice by extending vaccination guidance beyond the previous recommendation limited to influenza and pneumococcal vaccines (12). The inclusion of recommendations for Herpes Zoster and HPV vaccines, as well as considerations for live attenuated vaccines, underscores the importance of comprehensive vaccination strategies in the population with rheumatic diseases. Notably, achieving a stable disease state is no longer a prerequisite for vaccination, in accordance with the 2020 recommendations of European rheumatology societies (20), where vaccination was recommended not to be delayed due to disease activity. The ongoing relevance of SARS-CoV-2 infection and its associated disease, COVID-19, prompted the inclusion of specific recommendations for COVID-19 vaccination in this population. The rapidly evolving landscape of COVID-19 research and the need for timely, adaptable recommendations presented a particular challenge in developing these recommendations. This led to the development of good practice statements specifically addressing COVID-19 vaccination in rheumatologic patients, and they were based on a non-systematic review of the literature and expert consensus. While this approach allowed for quick dissemination of best practices, it also highlights the need for continuous updates as new evidence emerges. This is particularly important for patients with rheumatologic disease on high-dose glucocorticoids or other potent immunosuppressants, who are at increased risk for severe disease (21). Despite these advancements, this guideline has limitations. The literature review is limited to the end date of the research (30th June 2023), and thus does not account for subsequent studies that may impact these recommendations. However, at the time of writing this guideline, these recommendations are the most up-to-date available. Furthermore, most of the evidence is drawn from observational studies, and the low-quality evidence supporting the recommendation was prevalent. Finally, no studies exploring aspects of health economics were found. These limitations point out the necessity for future research to focus on the efficiency and safety of vaccines in patients with rheumatologic diseases, particularly in the context of immunosuppressive therapies.

In conclusion, this guideline provided a framework for the management of vaccinations in Italian patients with rheumatologic diseases, aiming to enhance clinical outcomes and reduce morbidity related to vaccine-preventable diseases. Future studies should prioritize high-quality, randomized controlled trials to address the current gaps in evidence, particularly regarding the safety and efficacy of various vaccination strategies in this complex patient population.

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