


POSITION ARTICLE AND GUIDELINES

Open Access



Guidelines on COVID-19 vaccination in patients with immune-mediated rheumatic diseases: a Brazilian Society of Rheumatology task force

Anna Carolina Faria Moreira Gomes Tavares¹, Ana Karla Guedes de Melo^{2*} , Vítor Alves Cruz³, Viviane Angelina de Souza⁴, Joana Starling de Carvalho¹, Ketty Lysie Libardi Lira Machado⁵, Lilian David de Azevedo Valadares⁶, Edgard Torres dos Reis Neto⁷, Rodrigo Poubel Vieira de Rezende⁸, Maria Fernanda Brandão de Resende Guimarães¹, Gilda Aparecida Ferreira¹, Alessandra de Sousa Braz², Rejane Maria Rodrigues de Abreu Vieira⁹, Marcelo de Medeiros Pinheiro⁷, Sandra Lúcia Euzébio Ribeiro¹⁰, Blanca Elena Gomes Rios Bica¹¹, Kátia Lino Baptista⁸, Izaias Pereira da Costa¹², Claudia Diniz Lopes Marques¹³, Maria Lúcia Lemos Lopes¹⁴, José Eduardo Martinez¹⁵, Rina Dalva Neubarth Giorgi¹⁶, Lícia Maria Henrique da Mota¹⁷, Marcos Antônio Araújo da Rocha Loures¹⁸, Eduardo dos Santos Paiva¹⁹, Odirlei André Monticielo²⁰, Ricardo Machado Xavier²⁰, Adriana Maria Kakehasi¹ and Gecilmara Cristina Salviato Pileggi⁷

Abstract

Objective: To provide guidelines on the coronavirus disease 2019 (COVID-19) vaccination in patients with immune-mediated rheumatic diseases (IMRD) to rheumatologists considering specific scenarios of the daily practice based on the shared-making decision (SMD) process.

Methods: A task force was constituted by 24 rheumatologists (panel members), with clinical and research expertise in immunizations and infectious diseases in immunocompromised patients, endorsed by the Brazilian Society of Rheumatology (BSR), to develop guidelines for COVID-19 vaccination in patients with IMRD. A consensus was built through the Delphi method and involved four rounds of anonymous voting, where five options were used to determine the level of agreement (LOA), based on the Likert Scale: (1) strongly disagree; (2) disagree; (3) neither agree nor disagree (neutral); (4) agree; and (5) strongly agree. Nineteen questions were addressed and discussed via teleconference to formulate the answers. In order to identify the relevant data on COVID-19 vaccines, a search with standardized descriptors and synonyms was performed on September 10th, 2021, of the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and LILACS to identify studies of interest. We used the Newcastle–Ottawa Scale to assess the quality of nonrandomized studies.

*Correspondence: anakarlagmelo@gmail.com

² Hospital Universitário Lauro Wanderley, Universidade Federal da Paraíba, R. Tab. Stanislau Eloy, 585 - Castelo Branco, João Pessoa, Paraíba 58050-585, Brazil

Full list of author information is available at the end of the article



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

Results: All the nineteen questions-answers (Q&A) were approved by the BSR Task Force with more than 80% of panelists voting options 4—agree—and 5—strongly agree—and a consensus was reached. These Guidelines were focused in SMD on the most appropriate timing for IMRD patients to get vaccinated to reach the adequate covid-19 vaccination response.

Conclusion: These guidelines were developed by a BSR Task Force with a high LOA among panelists, based on the literature review of published studies and expert opinion for COVID-19 vaccination in IMRD patients. Noteworthy, in the pandemic period, up to the time of the review and the consensus process for this document, high-quality evidence was scarce. Thus, it is not a substitute for clinical judgment.

Keywords: Covid-19 vaccination, Task force, Guidelines, Immune-mediated rheumatic diseases, Immunosuppression

Background

The pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), whose first case was described in Wuhan, China, in December 2019 [1], is the most significant health crisis being faced by humanity currently, and this has motivated efforts by the scientific community to seek ways to combat the transmission of this new virus. The virus has spread rapidly worldwide, with more than 228 million confirmed cases. In Brazil, it has resulted in more than 591,000 cumulative deaths, constituting one of the largest, if not the greatest, epidemiological tragedies in our history [2, 3].

Nowadays, four vaccines against SARS-CoV-2 are approved for use in Brazil: CoronaVac/Butantan Institute—inactivated—, ChAdOX1 nCoV19/Oxford/AstraZeneca/Oswaldo Cruz Foundation—viral vector—, BNT162b2mRNA/Pfizer—messenger RNA—and Janssen Vaccine—viral vector.

Although reports from several cohorts of patients with IMRD published around the world do not show an increased risk of unfavorable outcomes associated with coronavirus disease 2019 (COVID-19) compared to the general population [4], new data from population registries [5], including the Brazilian Registry of IMRD patients infected by the SARS-CoV-2 named ReumaCov, showed that patients with a moderate to a high degree of immunosuppression and those with an uncontrolled disease, especially systemic lupus erythematosus, systemic vasculitis and systemic sclerosis with pulmonary involvement, are at increased risk for COVID-19 outcomes or death (pulse therapy with methylprednisolone or cyclophosphamide [prevalence ratio, PR 2.86; 95% CI 1.59 to 5.14; $p < 0.018$]) [6].

Vaccination is the best way to avoid immune-preventable infectious diseases. Patients with IMRD may have a reduced immune response due to the underlying disease or immunosuppressive treatment. Therefore, they have a higher risk of infections, the leading causes of hospitalizations and deaths in this group of patients [7]. For this reason, the discussion on immunization against SARS-CoV-2 has become an urgent and relevant issue

[8]. The concern is shared about the effectiveness of different vaccines in patients with IMRD due to the disease itself and immunosuppressive drugs. Regarding the vaccine response, it is essential to emphasize that cellular and humoral immune responses are essential, and isolated response measures can lead to a mistaken idea of ineffectiveness [7].

Considering the uncertainties and the scarcity of data on the safety and efficacy of COVID-19 vaccination in patients with IMRD, the BSR Committee for Infectious and Endemic Diseases formed a task force composed of 24 rheumatologists to reach a consensus on COVID-19 vaccination using the Delphi method. This task force produced a consensus-based practical framework for COVID-19 vaccination in patients with IMRD. These recommendations are not intended to replace clinical judgment, and the vaccination decision should be individualized and shared between patients and rheumatologists.

Methods

Taskforce

The BSR first formed the task force with a steering committee that included the endemic and infectious diseases committee members and the executive board of the BSR. The task force was convened until July to August 2021 and comprised twenty-four rheumatologists: twenty rheumatologists specialized in treating diseases in adults and four pediatric rheumatologists from the BSR. The coordinator group, composed of nine rheumatologists, formulated a list of potential questions and a literature review. All nineteen concept questions were discussed and refined during two rounds of anonymous voting with other task force members. After questions approval, all nineteen answers were formulated by the coordinator group and then discussed in one round (3rd) with the whole group. In the last round (4th), all nineteen Q&A were voted. Each round consisted of the completion of a structured questionnaire to achieve a consensus.

Literature review

The research questions were defined according to the efficacy, immunogenicity, and safety of available COVID-19 vaccines in adult IMRD patients and the influence of immunosuppressive therapy on vaccine immunogenicity.

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS, using relevant descriptors and synonyms, adapting the search to the specifics of each database (Fig. 1). We also searched the Open Grey database, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and ClinicalTrials.gov to identify published, ongoing, and unpublished studies. All studies published before September 10th, 2021, were included, and no language restrictions were implemented for electronic search. Other papers that were considered relevant in the opinion of the experts could be added.

The search descriptors used for the Pubmed database were: "Rheumatic Diseases"[Mesh] OR "Autoimmune Diseases"[Mesh] OR "Connective Tissue Diseases"[Mesh] OR "Collagen Diseases"[Mesh] OR "Hereditary

Autoinflammatory Diseases"[Mesh] OR (chronic immune inflammatory diseases) OR (immune-mediated inflammatory diseases) AND "COVID-19 Vaccines"[Mesh] OR "mRNA-1273 vaccine" [Supplementary Concept] OR "ChAdOx1 COVID-19 vaccine" [Supplementary Concept] OR "Ad5-nCoV vaccine" [Supplementary Concept] OR "Ad26.COV2.S vaccine" [Supplementary Concept] OR "BNT162 vaccine" [Supplementary Concept]. The search descriptors were adapted for each database used in this literature review.

The database search yielded 780 records. We also included two additional records. After removing duplicates, titles and abstracts were examined. We retrieved 52 full-text articles for further scrutiny; of those, 25 studies were excluded due to: ineligible population (n=10), preprint (n=2), not reporting patient data (n=11), or no full text available (n=2) (Fig. 1). We finally included 27 studies in this review [9–30].

Studies were eligible if they presented data on the immunogenicity, effectiveness, and/or safety of the COVID-19 vaccine in patients with IMRD. We used The

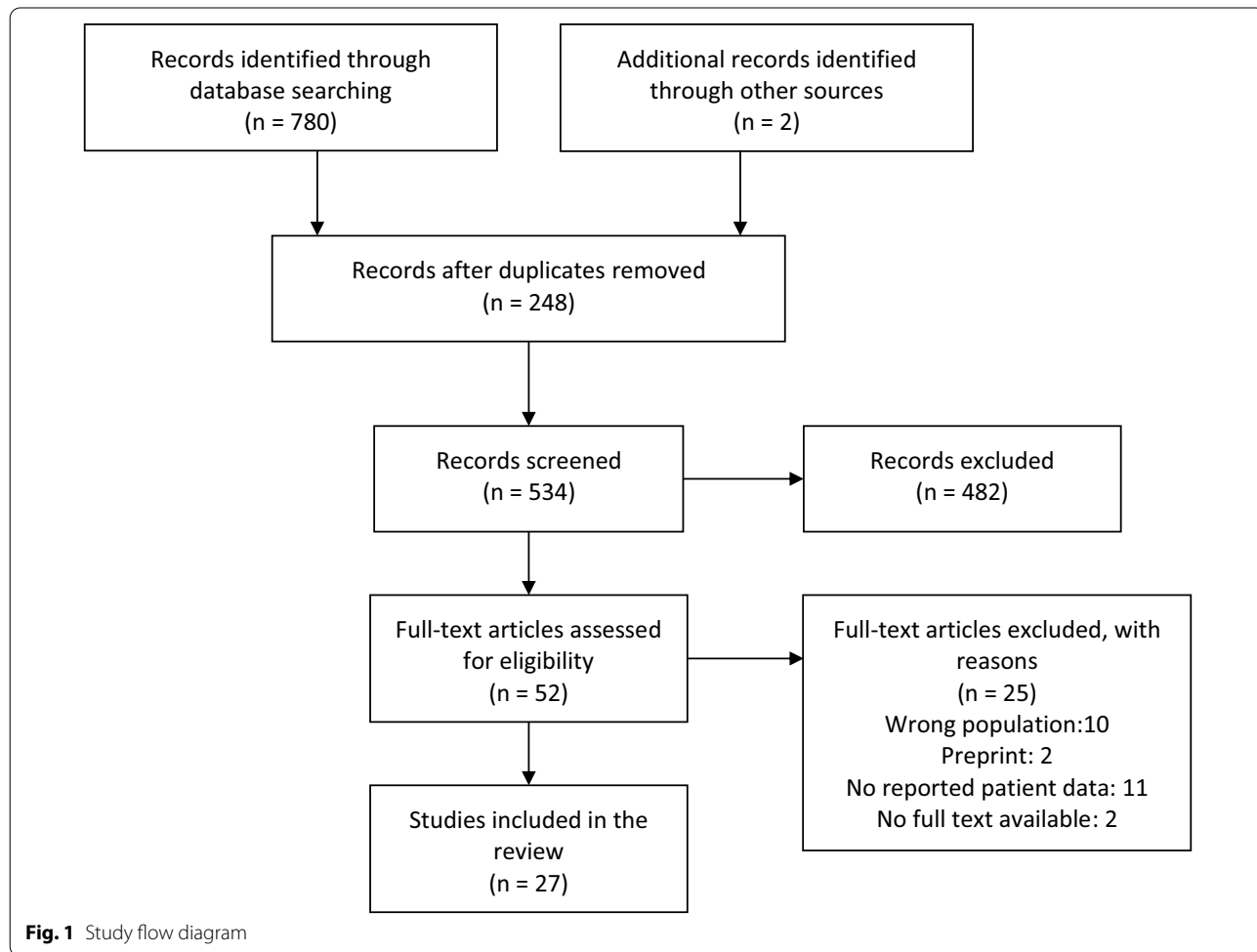


Fig. 1 Study flow diagram

Table 1 Recommendations related to COVID-19 vaccination in patients with immune-mediated rheumatic diseases

Recommendations	LOA
1. Based on their risk for COVID-19, patients with IMRD should be encouraged to get their COVID-19 vaccination in a shared-making decision process	100%
2. The decision on the best timing to be vaccinated with COVID-19 vaccines should be individualized, considering the patient's age, the underlying IMRD, and its treatment, aiming to optimize the vaccine response	100%
3. COVID-19 vaccination should ideally occur in the setting of stable disease activity in patients with IMRD and absence or low immunosuppression	95.9%
4. The rheumatologist should inform their patients on the possibility of not effective vaccine response, especially those under high immunosuppression	100%
5. Immunomodulatory or immunosuppressive treatment in patients with IMRD should not be discontinued before and or after receiving COVID-19 vaccines, except for B-cell depleting agents (e.g., rituximab)	95.8%
6. COVID-19 vaccination should be ideally done 6 months after the last dose of rituximab and four weeks before the next one considering the complete vaccination schedule *If this is not possible, this recommendation should be followed at least for the first dose	95.8%
7. IMRD patients should receive the same COVID-19 vaccine platform in the complete schedule *In cases of severe adverse events (anaphylaxis) or immediate reactions (urticaria, angioedema, or respiratory distress) to any vaccine platform, an alternative approach is recommended for additional doses following local availability	95.8%
8. An additional dose of the COVID-19 vaccine should be considered for patients with IMRD who completed their vaccination schedule	100%
9. The additional dose should preferably be with a COVID-19 vaccine platform different than that used in the primary COVID-19 vaccination schedule	95.8%
10. Temporary interruption of immunomodulatory drugs before an additional dose of COVID-19 vaccines for patients with IMRD should not be recommended	91.7%
11. Temporary interruption of rituximab should not be recommended concerning the COVID-19 vaccine additional dose *Until high-quality evidence is available	83.4%
12. COVID-19 vaccines can be administered simultaneously with the other vaccines	92.3%
13. Assessment for seroconversion after COVID-19 vaccination is not recommended	95.9%
14. Seasonal influenza and pneumococcus vaccination are strongly recommended for patients with IMRD * It is essential to keep vaccination cards updated	92.3%
15. Vector viral COVID-19 vaccine should be recommended for patients with IMRD and thrombocytopenia or previous thrombotic events	95.9%
16. Pregnant patients with IMRD should receive only non-vector viral COVID-19 vaccines *Until new safety evidence is available for this scenario	100%
17. Children and adolescents (12–17 years) with IMRD should receive COVID-19 vaccination	95.8%

IMRD: immune-mediated rheumatic diseases

Newcastle–Ottawa Scale (NOS) [31] (Additional file 1) to assess the methodological quality of the included studies.

Consensus building

The entire process was conducted following the Delphi method, a well-established method for consensus-building [32, 33], and included four rounds of anonymous voting. Each round consisted of voting a structured online questionnaire built on the Google® Forms platform, and task force members received the questionnaire by e-mail. Based on the Likert Scale, all members should indicate their LOA for question–answer: 1. Strongly disagree; 2. Disagree; 3. Neither agree nor disagree (neutral); 4. Agree; and 5. Strongly agree. The first round consisted in discussing all questions with all members justifying agreement or disagreement to the questions. In the second round, the convener and collaborators made modifications considered plausible. All questions were voted according to the LOA mentioned above. In the third

round, questions and answers were voted, and task force members had to justify agreement or disagreement for each Q&A; in the last round (4th), the coordinator group applied suggested modifications, and task force members voted statements-answers according to the LOA. More than 80% of panelists voted for options 4—agree—and 5—strongly agree in all scenarios, and the consensus was achieved, considering the LOA previously established by the coordinator group and following Delphi methodology. The manuscript was drafted and revised by all the task force members, and seventeen recommendations (Table 1) were established.

Recommendations Questions to explore

1. Should patients with IMRD receive COVID-19 vaccines?

Yes. Rheumatologists should be familiar with and be up to date on the characteristics, efficacy, and safety of COVID-19 vaccines to better guide their patients, considering both the local epidemiological situation and the risks and benefits of this SMD process.

LOA: 95.8% Strongly agree; 4.2% Agree

2. Should the decision on the best timing to get COVID-19 vaccination for patients with IMRD be individualized and preferably shared with the rheumatologist, considering the patient's age, the underlying IMRD, and its treatment, aiming to optimize the vaccine response?

Yes. Some factors, such as old age and comorbidities (mainly heart disease and chronic lung disease), are associated with unfavorable outcomes and a worse prognosis of COVID-19. The attending physician should consider IMRD activity and the degree of immunosuppression to determine the most appropriate time for COVID-19 vaccination in this population. In addition, rheumatologists should determine whether the patient fits the risk group for priority vaccination, as defined by the Public Health Agencies.

LOA: 83.3% Strongly agree; 16.7% Agree

3. Should the rheumatologist discuss with their patients the possibility of lower vaccine response, especially those under a high degree of immunosuppression?

Yes. Despite the scarcity of studies and the significant variability of immunosuppressants used in clinical practice, recent evidence suggests that patients under intense immunosuppression may have a lower vaccine response. Particular attention should be given to patients using doses greater than 20 mg/day of glucocorticoids and those using abatacept or rituximab due to their negative impact on vaccine response [34–37].

LOA: 83.3% Strongly agree; 16.7% Agree

4. Should the IDEAL timing get COVID-19 vaccination in patients with IMRD be when in remission or absence or low degree of immunosuppression?

Yes. Aiming for better vaccine response, IMRD patients should be vaccinated when in remission or under control with a low degree of immunosuppression or without immunosuppressive treatment [38–40]. In other situations, it is worth discussing with the attending rheumatologist on the best timing for vaccination, considering the epidemiological situation and the inclusion in the priority groups defined by the Ministry of Health and the

associated factors specific to IMRD that are described above.

LOA: 79.2% Strongly Agree; 16.7% Agree

5. Based on the available literature data, should immunomodulatory/immunosuppressive treatment in patients with IMRD not be discontinued before and or after receiving COVID-19 vaccines? Should COVID-19 vaccination in IMRD patients be postponed while under treatment with a B-cell depleting agent (e.g., rituximab)?

Yes. To date, there are no available data to guide the management of immunosuppressive therapy in the context of COVID-19 vaccination. All the currently approved vaccines are non-live, and there is no risk of vaccine-related infection. It is also necessary to consider the risk of reactivation of the underlying disease with the interruption of a specific treatment and the potential negative effect of using immunosuppressive medications on vaccine response. Two studies recently published addressed COVID-19 vaccination in patients with IMRD. Braun-Moscovici et al. conducted a phase IV, prospective open-label trial to assess the humoral response after two doses of mRNA COVID-19 vaccine in patients with IMRD treated with immunomodulatory drugs and the impact on IMRD activity [34]. After multivariate logistic regression analysis, rituximab (RTX) and abatacept were related to decreased humoral response to a vaccine. The authors concluded that most disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), biologics, and Janus Kinase (Jak) inhibitors, can be continued with BNT162b2mRNA/Pfizer COVID-19 vaccine. Delaying treatment with RTX, when possible, should be considered in individual cases. Mrak et al. [35] evaluated humoral and cellular immune responses in RTX treated patients following COVID-19 vaccination. Twenty-nine (39%) out of 74 RTX treated patients seroconverted with BNT162b2mRNA/Pfizer immunization. Twenty-six out of 45 patients (58%) had a detectable cellular response. These data suggest that vaccination can induce SARS-CoV-2 specific antibodies in RTX-treated patients regardless of humoral response and may lead to new vaccination strategies in patients treated with RTX. A Brazilian study evaluated the immunogenicity and safety of the CoronaVac inactivated vaccine in patients with IMRD in a phase IV trial [36]. Lower anti-SARS-CoV2 IgG seroconversion (70.4 versus 95.5%, $p < 0.001$) and neutralizing antibodies positivity (NAbs) (56.3 versus 79.3%, $p < 0.001$) in the IMRD group compared to the control group were evidenced. The use of MTX (OR 0.42; 95% CI 0.29–0.61, $p < 0.001$), mycophenolate mofetil (OR 0.15; 95% CI 0.09–0.24, $p < 0.001$), tumor necrosis factor-alpha inhibitors

(OR 0.41; 95% CI 0.26–0.64, $p < 0.001$), abatacept (OR 0.24; 95% CI 0.13–0.46, $p < 0.001$) and RTX (OR 0.34; 95% CI 0.13–0.93, $p = 0.036$) were associated with lower seroconversion in patients with IMRD. MTX (OR 0.67, 95% CI 0.47–0.95, $p = 0.024$), mycophenolate mofetil (OR 0.33; 95% CI 0.21–0.53, $p < 0.001$) and RTX (OR 0.28; 95% CI 0.09–0.87, $p = 0.028$) were associated with the absence of neutralizing activity in patients with IMRD. Together, these data provided evidence of humoral and cellular immunogenicity in a short-term follow-up of IMRD patients vaccinated with mRNA and inactivated COVID-19 vaccines. Long-term data is required. COVID-19 vaccination should be ideally done 6 months after the last dose of RTX and four weeks before the next one considering the complete schedule. If this is not possible, this recommendation should be followed, at least for the first dose.

LOA: 50% Strongly Agree; 45.8% Agree

6. Should COVID-19 vaccination be recommended for patients with IMRD even if they have already been infected with this virus?

Yes. Regardless of the scarcity of evidence about acquired immunity duration due to SARS-CoV-2 infection and the formal recommendation for vaccination of recovered patients from the general population, we recommend following the local health agencies' guidelines until new evidence or recommendations are available. Cases of reinfection in humans or infection with new virus variants have been reported a few months after initial infection, challenging the idea of long-lasting protective immunity [41–43]. In addition, it is crucial to consider the scenario of the emergence of new virus variants.

LOA: 87.5% Strongly agree; 8.3% Agree

7. Should all platforms of COVID-19 vaccines be considered potentially safe for vaccination of patients with IMRD?

Yes. None of the platforms used to produce vaccines contain live viruses. Recently published studies [34–37] that assessed efficacy and safety of vaccines in patients with IMRD showed a low incidence of adverse events, most of them being local and self-limited. Guidelines from local health agencies should be followed until new evidence are available.

LOA: 70.8% Strongly agree; 29.2% Agree

8. Should the choice of COVID-19 vaccine for IMRD patients follow the recommendations of local regulatory agencies and availability?

Yes. The choice should follow the requirements of local public health agencies and the local availability of the vaccines. We recommend that all individuals, including patients with IMRD, receive a COVID-19 vaccine that has undergone a rigorous national regulatory process and is approved.

LOA: 83.3% Strongly agree; 16.7% Agree

9. Should IMRD patients receive the same platform in the complete schedule of COVID-19 vaccination until new evidence about interchangeability is available?

Yes. The entire vaccination schedule must follow the same platform initially used and should follow the national and local health regulatory agencies' guidelines. In cases of severe adverse events (anaphylaxis) or immediate reactions (urticaria, angioedema, or respiratory distress) to any vaccine platform [44], an alternative approach is recommended for additional doses following local availability. Recently the National Immunization Program (NIP) recommended an additional dose of COVID-19 vaccine for immunocompromised patients, whose platform choice should be guided by local availability but should be different from the platform of the initial schedule [45].

LOA: 62.5% Strongly agree; 33.3% Agree

10. Should an additional dose of the COVID-19 vaccine be considered for patients with IMRD who completed their vaccination schedule?

Yes. To date, studies indicated that individuals with moderately to severely compromised immune systems may not build the same level of immunity to a 2-dose vaccine schedule compared to people who are not immunocompromised [32–35]. Therefore, they may benefit from an additional dose to ensure better protection against COVID-19. In addition, data on breakthrough infections have accounted for a large proportion of the hospitalization rate from fully vaccinated immunocompromised subjects [46].

LOA: 83.3% Strongly agree; 16.7% Agree

11. Should the additional dose preferably be with a COVID-19 vaccine platform different than that used in the primary COVID-19 vaccination schedule?

Yes. Available data on the responses to heterologous COVID-19 vaccination, especially in countries using inactivated and vector viral vaccines, showed higher spike RBD-IgG (receptor binding domain) and neutralizing activities than the homologous vaccine recipients [47–49].

LOA: 62.5% Strongly agree; 33.3% Agree

12. Should a temporary interruption of immunomodulatory drugs be recommended before an additional dose of COVID-19 vaccines for patients with IMRD?

No. Long-term data are required to guide recommendations for immunomodulatory/immunosuppressive drugs interruption and COVID-19 vaccination. So far, the literature data is conflicting and does not allow to take a definitive position.

LOA: 37.5% Strongly agree; 54.2% Agree

13. Should rituximab be interrupted concerning COVID-19 vaccine additional dose?

No. Regarding rituximab or other anti-CD20 therapies, the best period for vaccination must be discussed through an SMD process between the patient and assistant rheumatologist. Assessing serum CD19 levels [40] could be a tool to guide the best timing for the additional dose of the vaccine and subsequent dose of rituximab. If this is not available, it is recommended to perform the additional dose 2 to 4 weeks before the next dose of RTX. The available literature points out a possible influence of rituximab in seroconversion [32–36, 50], but more information is required.

LOA: 29.2% Strongly agree; 54.2% Agree

14. Is there a risk that the underlying disease will worsen or reactivate after COVID-19 vaccination?

Yes. Natural viral infection or vaccination have been noted as potential triggering events for inflammatory diseases for many decades. Regarding disease activity of IMRD and vaccination, it is suggested that promoting vaccination in quiescent disease phases avoids disease flare-up and favors a better immune response. However, due to COVID-19 severity, a rapid COVID-19 immunization is strongly recommended, and the patients included in most trials were vaccinated in different activity phases of their disease. Concerning the possibility of inducing or enhancing the autoimmune response through molecular mimicry between the viral antigen and host antigen, Rotondo et al. showed a low rate (5.7%) of disease relapse of IMRD after the first dose of vaccine, the rate of disease flare-up observed after BNT162b2mRNA/Pfizer vaccination could be due to the higher frequency of this vaccine administration. However, no significant differences in adverse events (AEs) between BNT162b2mRNA/Pfizer and ChAdOx1 nCoV19 were found in this study [51]. Watad et al. reported that the average time between vaccination and new-onset or flare of symptoms was four days (median of 4 days [1–25 days] in those who developed an IMRD after the first dose and a median of 4 days

[1–7 days] in those after the second dose) with most cases occurring after the first inoculation (77.8%) [52]. Despite the high population exposure in the regions served by these centers, the authors concluded that IMRDs flares or onset temporally associated with COVID-19 vaccination appear rare. Most are moderate events and respond to therapy; although some severe flares occurred, new studies could be necessary.

LOA: 66.7% Strongly agree; 29.2% Agree

15. Is it recommended to assess for seroconversion after COVID-19 vaccination?

No. It is not recommended to assess the post-vaccination humoral response against SARS-CoV-2. The level of seroconversion varies among individuals, especially those immunocompromised. In addition, humoral immunity is not the only protective barrier against SARS-CoV-2, and the durability of the protection provided by natural infection and vaccination is not well-defined [35]. Individuals that received COVID-19 vaccines or those who recovered from infection should be informed that the durability of the protection is still to be determined.

LOA: 79.2% Strongly agree; 16.7% Agree

16. Should patients with IMRD also receive influenza and pneumococcus vaccines?

Yes. Vaccination against seasonal influenza and pneumococcus is strongly recommended for patients with IMRD, considering the risk of severe pneumonia in immunocompromised patients. COVID-19 vaccines can be administered with other vaccines at the same time, accordingly to National Immunization Program and the Ministry of Health [53]. We emphasize that it is important to keep IMRD patients vaccination card updated.

LOA: 73.1% strongly agree; 19.2% agree

17. Should vector viral vaccine be recommended for patients with IMRD and thrombocytopenia or previous thrombotic events?

Yes. Thromboembolic events related to viral vector vaccines are rare, with an average of 2 to 4 cases reported per million doses applied. Its immunological mechanism is described in immune-mediated thrombotic thrombocytopenia induced by heparin (HITT or HIT type 2), where thrombosis and thrombocytopenia are associated with anti-platelet factor IV antibodies. Although the risk factors for developing this adverse reaction are unknown, most cases were observed in women under 50 years old, without comorbidities or risk factors for thrombosis. There is no evidence of greater risk among IMRD patients and no plausible

reason to contraindicate COVID-19 vaccination in this group. Vector viral vaccines should be avoided in individuals with a previous history of HITT and venous and or arterial thrombosis cases with thrombocytopenia after any vaccine [54–58].

LOA: 54.2% Strongly agree; 41.7% Agree

18. Should pregnant patients with IMRD receive only non-vector COVID-19 vaccines until new safety evidence is available for this scenario?

Yes. Vaccination should be encouraged in pregnant women [59], following guidelines of national health authorities. Since the notification of a fatal case of thrombosis with thrombocytopenia in a pregnant woman after the ChAdOx1- nCoV19 vaccine, the National Health Surveillance Agency and the Brazilian Ministry of Health discontinued the administration of vector viral vaccines in pregnant and postpartum women. Until such association is definitively clarified, Brazilian regulatory agencies recommended only m-RNA and inactivated virus COVID-19 vaccines for this group of individuals.

LOA: 58.3% Strongly agree; 41.7% Agree

19. Should children and adolescents (12–17 years old) with IMRD be vaccinated against SARS-CoV-2?

Yes. On June 23rd, 2021, the Center for Disease Control and Prevention reported an increased number of post-mRNA vaccine myocarditis/pericarditis cases (possibly hypersensitivity eosinophilic myocarditis). These are considered rare events, with no reported fatal outcomes. The majority of cases occurred in adolescents and young adults (under 30 years old), mainly boys over 12 to 17 years old. There are no long-term data on this outcome yet [60]. The BSR considers the benefits to outweigh the risks and recommends COVID-19 vaccination for this age group. LOA: 70.8% Strongly agree; 25% Agree.

Discussion

This document presents the result of a BSR Task Force Delphi consensus-building to provide guidelines for COVID-19 vaccination in IMRD patients based on clinical scenarios. The consensus process considered potential concerns and was elaborated according to evidence-based information and expert opinion. The BSR developed these guidelines with a high LOA among their panelists regarding COVID-19 vaccination in patients with IMRD. These recommendations (Table 1) included discussion about particularities of safety and immunogenicity of vaccination in immunocompromised patients, considering adverse events and guidance for managing immunosuppressive treatment.

Vaccination is the most effective strategy to reduce and mitigate the SARS-CoV-2 pandemic. In randomized studies, COVID-19 vaccines proved efficacy in reducing SARS-CoV-2 infection rates and severe disease. However, the pivotal studies did not include IMRD patients who have an immune dysfunction related either to the underlying disease or the use of immune-modulating drugs, which could interfere in COVID-19 vaccination response. Both humoral and T-cell immune response following vaccination are relevant to evaluate effectiveness. Understanding of the development and durability of these responses determines the necessity for booster dosing schedules [34–37]. Currently, data have shown a lower response rate in IMRD patients when compared to healthy controls. It is unclear whether this is attributable to the underlying disease or its different treatments [38, 61].

The decision to vaccinate IMRD patients should be individualized and preferably shared between health professionals and patients, considering the epidemiological setting, the immunosuppression degree, and disease activity. Immunization should not be delayed in epidemics and pandemics such as COVID-19 since the benefits outweigh the risks. Misinformation negatively affects the decision to vaccinate, reduces the population's confidence, and decreases adherence to vaccination. SDM process should be based on highest scientific evidence and on persuasive and motivational approach strategies especially among pregnant women, children, adolescents and immunocompromised patients. This could be made discussing with patients risks and benefits of vaccines, listening to their doubts, clarifying their concerns and providing them ways to get high-quality information from confident sources. It seems to be the most suitable way to overcome barriers to vaccine hesitation, especially in vulnerable populations [62–65].

Vaccination hesitancy is a complex and multifactorial phenomenon defined as a delay in the acceptance of vaccination despite the availability of vaccination services. A study recently published by our group analyzed data from 1,000 patients with IMRD and evidenced a high vaccine acceptance rate (81.9%), but also found out that 25% of patients who hesitated to receive the COVID vaccine linked their decision to the lack of a definitive recommendation for vaccination against COVID-19, suggesting that physicians should be more engaged in disseminating information demystifying issues related to vaccination [64, 65].

All four COVID-19 vaccines approved in Brazil are non-live, and thus, there is no risk of inducing vaccine-related disease [51, 52]. Several studies confirmed that other non-live vaccines, such as those against influenza, pneumococcus, hepatitis A, hepatitis B, and human

papillomavirus, are effective and safe for this population [66, 67]. Influenza and pneumococcus vaccinations are strongly recommended for IMRD patients because of an increased risk of developing severe pneumonia and its complications such as severe respiratory distress and respiratory failure [39, 66–69].

Some international Rheumatology Societies have released recommendations for COVID-19 vaccination in IMRD patients. The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) suggested that SMD process is essential in defining the best timing for vaccination and stand out the absence of safer and more effective vaccine platform for individuals with IMRD. The ACR pointed to temporary interruption of immunosuppressive agents before and/or after immunization, such as abatacept, MTX, and Jak inhibitors. This clinical guidance was based on observational studies assessing vaccination responses against other microorganisms, such as pneumococcus and influenza, and in the growing knowledge about the impact of immunosuppressants in COVID-19 vaccines responses. The use of new technologies, such as mRNA and viral vector-based, is relatively new, and the impact of the underlying disease and immune-modulating drugs on serological and T-cell responses are uncertain [7, 34–37]. The authors recognized that there is limited high-quality evidence to base these recommendations [39, 40].

Given this scenario of uncertainty, we performed a systematic literature review on the safety and efficacy of COVID-19 vaccines. Only non-randomized studies were found with heterogeneous subtypes of IMRD and diverse treatments regimens, absence of a well-defined control group, and differences in outcomes, leading to difficulties in interpreting the results and comparing the studies. We performed critical judgment of the included studies based on the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome using the Newcastle–Ottawa Scale.

Systematic reviews of prospective cohort studies could be the key to better understanding the effectiveness and safety of the COVID-19 vaccine in IMRD patients. We believe that the results of our review and recommendations may help decision-making processes and guide Brazilian rheumatologists in daily practice.

Conclusion

The BSR task force approved a twenty Q&A with more than 80% LOA, considering scenarios of daily practice to help the decisions on COVID-19 vaccination in

IMRD patients based on the SMD process and established seventeen recommendations (Table 1).

Although these guidelines are based on the best evidence available on the safety and immunogenicity of COVID-19 vaccines in patients with IMRD, we emphasize that there is still no high-quality evidence to guide the temporary withdrawal of immunomodulatory or immunosuppressive medications before or after COVID-19 vaccination and further research is required. It is noteworthy that the current consensus was built based on expert opinion and thus, do not intend to substitute clinical judgment. These Guidelines will be updated, As soon as new evidence about the COVID-19 vaccines' safety and efficacy emerges.

Abbreviations

ACR: American College of Rheumatology; BSR: Brazilian Society of Rheumatology; CG: Control group; COVID 19: Coronavirus disease 2019; DMARDs: Disease-modifying rheumatic drugs; EULAR: European Alliance of Associations for Rheumatology; IgG: Immunoglobulin G; IMRD: Immune-mediated rheumatic diseases; JAK: Janus kinase; LOA: Level of agreement; MTX: Methotrexate; mRNA: Ribonucleic acid messenger; NAb: Neutralizing antibody; NIP: National Immunization Programme; PR: Prevalence ratio; Q&A: Questions-answers; RBD: Receptor binding domain; ReumaCoV: Brazilian Registry of IMRD patients infected by the SARS-CoV-2; RTX: Rituximab; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SMD: Shared-making decision process; YF: Yellow fever.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s42358-022-00234-7>.

Additional file 1. Newcastle–Ottawa Quality Assessment Scales.

Acknowledgements

Not applicable.

Authors' contributions

All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Nor applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. ²Hospital Universitário Lauro Wanderley, Universidade Federal da Paraíba, R. Tab. Stanislaw Eloy, 585 - Castelo Branco, João Pessoa, Paraíba

58050-585, Brazil. ³Hospital das Clínicas, Universidade Federal de Goiás, Goiânia, Brazil. ⁴Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil. ⁵Hospital Universitário Cassiano Antônio Moraes, Universidade Federal do Espírito Santo, Vitória, Brazil. ⁶Hospital Getúlio Vargas, Recife, Brazil. ⁷Universidade Federal de São Paulo, São Paulo, Brazil. ⁸Universidade Federal Fluminense, Niterói, Brazil. ⁹Hospital Geral, Fortaleza, Brasil. ¹⁰Universidade Federal do Amazonas, Manaus, Brazil. ¹¹Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. ¹²Faculdade de Medicina, Universidade Federal do Mato Grosso do Sul, Campo Grande, Brazil. ¹³Universidade Federal de Pernambuco, Recife, Brazil. ¹⁴Universidade Federal de Ciências da Saúde, Porto Alegre, Brazil. ¹⁵Pontifícia Universidade Católica, São Paulo, Brazil. ¹⁶Instituto de Assistência Médica ao Servidor Público Estadual, São Paulo, Brazil. ¹⁷Hospital Universitário, Brasília, Brazil. ¹⁸Universidade Estadual, Maringá, Brazil. ¹⁹Hospital das Clínicas, Universidade Federal do Paraná, Curitiba, Brazil. ²⁰Hospital das Clínicas, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Received: 16 March 2021 Accepted: 8 January 2022

Published online: 17 January 2022

References

- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China Lancet*. 2020;395(10223):497–506.
- Retrieved from: <https://covid.saude.gov.br> [cited 09/14/2021]
- Retrieved from: <https://www.paho.org/pt/covid19> [cited 09/14/2021]
- Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis*. 2020;79(5):667–8.
- Pablos JL, Galindo M, Carmona L, Lledó A, Retuerto M, Blanco R, et al. Clinical outcomes of hospitalized patients with COVID-19 and chronic inflammatory and immune-mediated rheumatic diseases: a multicentric matched cohort study. *Ann Rheum Dis*. 2020;79(12):1544–9.
- Marques CDL, Kakehasi AM, Pinheiro MM, Mota LMH, Albuquerque CP, Silva CR, et al. High levels of immunosuppression are related to unfavorable outcomes in hospitalized patients with rheumatic diseases and COVID-19: first results of ReumaCoV Brasil registry. *RMD Open*. 2021;7(1):e001461.
- Jena A, et al. Response to SARS-CoV-2 vaccination in immune-mediated inflammatory diseases: Systematic review and meta-analysis. *Autoimmun Rev*. 2021. <https://doi.org/10.1016/j.autrev.2021.102927>.
- Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: The status and perspectives in delivery points of view. *Adv Drug Deliv Rev*. 2020;170:1–25.
- Seyahi E, Bakhdiyari G, Oztas M, Kuskucu MA, Tok Y, Sut N, et al. Antibody response to inactivated COVID-19 vaccine (CoronaVac) in immune-mediated diseases: a controlled study among hospital workers and elderly. *Rheumatol Int*. 2021;41(8):1429–40. <https://doi.org/10.1007/s00296-021-04910-7>.
- Michiels Y, Houhou-Fidouh N, Collin G, Berger J, Kohli E. Impact of low-dose methotrexate-adalimumab combination therapy on the antibody response induced by the mRNA-1273 SARS-CoV-2 vaccine: case of an elderly patient with rheumatoid arthritis. *Vaccines*. 2021;9(8):883. <https://doi.org/10.3390/vaccines9080883>.
- Veenstra J, Wang J, McKinnon-Maksimowicz K, Liu T, Zuniga B, Hamzavi I, et al. Correspondence on "Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort." *Ann Rheum Dis*. 2021;80(10): e160. <https://doi.org/10.1136/annrheumdis-2021-220736>.
- Izmirly PM, Kim MY, Samanovic M, Fernandez-Ruiz R, Ohana S, Deonaraïne KK, et al. Evaluation of immune response and disease status in SLE patients following SARS-CoV-2 vaccination. *Arthritis Rheumatol*. 2021. <https://doi.org/10.1002/art.41937>.
- Prendecki M, Clarke C, Edwards H, McIntyre S, Mortimer P, Gleeson S, et al. Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. *Ann Rheum Dis*. 2021;80(10):1322–9. <https://doi.org/10.1136/annrheumdis-2021-220626>.
- Cherian S, Paul A, Ahmed S, Alias B, Manoj M, Santhosh AK, et al. Safety of the ChAdOx1 nCoV-19 and the BBV152 vaccines in 724 patients with rheumatic diseases: a post-vaccination cross-sectional survey. *Rheumatol Int*. 2021;41(8):1441–5. <https://doi.org/10.1007/s00296-021-04917-0>.
- Cuomo G, Attenu M, Naclerio C, et al. POS1248 safety profile of pfizer-biontech covid-19 vaccine in patients with rheumatic diseases: preliminary assessment. *Ann Rheum Dis*. 2021;80:907–8.
- Chiang TP, Connolly CM, Ruddy JA, et al. Antibody response to the Janssen/Johnson & Johnson SARS-CoV-2 vaccine in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis*. 2021;80:1365–6.
- Benucci M, Damiani A, Infantino M, Manfredi M, Grossi V, Lari B, et al. Presence of specific T cell response after SARS-CoV-2 vaccination in rheumatoid arthritis patients receiving rituximab. *Immunol Res*. 2021;69(4):309–11. <https://doi.org/10.1007/s12026-021-09212-5>.
- Niebel D, Raiser-Isselstein V, Jäschke K, Braegelmann C, Bieber T, Wenzel J. Exacerbation of subacute cutaneous lupus erythematosus following vaccination with BNT162b2 mRNA vaccine. *Dermatol Ther*. 2021;34(4): e15017. <https://doi.org/10.1111/dth.15017>.
- Benucci M, Infantino M, Manfredi M, Li Gobbi F, Sarzi-Puttini P, Caproni M. Covid vaccination in patients with autoimmune diseases treated with mycophenolate: Let's think back to the recommendations. *Autoimmun Rev*. 2021;20(10): 102908. <https://doi.org/10.1016/j.autrev.2021.102908>.
- Terracina KA, Tan FK. Flare of rheumatoid arthritis after COVID-19 vaccination. *Lancet Rheumatol*. 2021;3(7):e469–70. [https://doi.org/10.1016/S2665-9913\(21\)00108-9](https://doi.org/10.1016/S2665-9913(21)00108-9).
- Ammitzbøll C, Bartels LE, Bøgh Andersen J, Risbøl Vils S, Elbaek Mistegård C, Dahl Johannsen A, et al. Impaired antibody response to the BNT162b2 messenger RNA coronavirus disease 2019 vaccine in patients with systemic lupus erythematosus and rheumatoid arthritis. *ACR Open Rheumatol*. 2021;3(9):622–8. <https://doi.org/10.1002/acr2.11299>.
- Machado PM, Lawson-Tovey S, Hrych K, et al. LB0002 COVID-19 vaccine safety in patients with rheumatic and musculoskeletal disease. *Ann Rheum Dis*. 2021;80:199–200.
- Bixio R, Bertelle D, Masia M, Pistillo F, Carletto A, Rossini M. Incidence of disease flare after BNT162b2 coronavirus disease 2019 vaccination in patients with rheumatoid arthritis in remission. *ACR Open Rheumatol*. 2019. <https://doi.org/10.1002/acr2.11336>.
- Bartels LE, Ammitzbøll C, Andersen JB, Vils SR, Mistegaard CE, Johannsen AD, et al. Local and systemic reactogenicity of COVID-19 vaccine BNT162b2 in patients with systemic lupus erythematosus and rheumatoid arthritis. *Rheumatol Int*. 2021. <https://doi.org/10.1007/s00296-021-04972-7>.
- Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS-CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis*. 2021;80:1357–9.
- Boyarisky BJ, Ruddy JA, Connolly CM, et al. Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis*. 2021;80:1098–9.
- Sattui SE, Liew JW, Kennedy K, Siroitch E, Putman M, Moni TT, et al. Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. *RMD Open*. 2021;7(3): e001814. <https://doi.org/10.1136/rmdopen-2021-001814>.
- Prendecki M, Clarke C, Edwards H, et al. Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. *Ann Rheum Dis*. 2021;80:1322–9.
- Braun-Moscovici Y, Kaplan M, Braun M, et al. Disease activity and humoral response in patients with inflammatory rheumatic diseases after two doses of the Pfizer mRNA vaccine against SARS-CoV-2. *Ann Rheum Dis*. 2021;80:1317–21.
- Salviani C, Scolari F, Alberici F. Correspondence on "Immunogenicity and safety of anti-SARS-Cov-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort." *Ann Rheumatic Dis*. 2021;80:e158.
- Wells G, Shea B, O'Connell D et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. *Ottawa, Ontario: The Ottawa Health Research Institute*, 2011.
- Steuer J. The Delphi method: An efficient procedure to generate knowledge. *Skelet Radiol*. 2011;40(8):959–61.
- Boukded R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators:

- a systematic review. *PLoS ONE* 2011;6(6): 1204. <https://doi.org/10.1371/journal.pone.0020476>
34. Braun-Moscovici Y, Kaplan M, Markovits D, Giryès S, Toledano K, Tavor Y et al. Humoral response to Pfizer mRNA vaccine against SARS CoV2, in patients with autoimmune inflammatory rheumatic diseases and the impact on the rheumatic disease activity. <https://doi.org/10.1101/2021.04.02.21254493>.
 35. Mrak D, Tobudic S, Koblischke M, Granninger M, Radner H, Sieghart D, et al. SARS-CoV-2 vaccination in rituximab-treated patients: B cells promote humoral responses in the presence of T-cell-mediated immunity. *Ann Rheum Dis*. 2021. <https://doi.org/10.1136/annrheumdis-2021-220781>.
 36. Medeiros-Ribeiro AC, Aikawa NE, Saad CGS, et al. Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. *Nat Med*. 2021.
 37. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis*. doi: <https://doi.org/10.1136/annrheumdis-2021-2206>
 38. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 Update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2020;79(1):39–52.
 39. Bijlsma JWJ. EULAR December 2020 viewpoints on SARS-CoV-2 vaccination in patients with RMDs. *Ann Rheum Dis*. 2020;2021:2020. <https://doi.org/10.1136/annrheumdis-2020-219773>.
 40. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases—Version 3. *Arthritis Rheumatol*. 2021. <https://doi.org/10.1002/art.41928>.
 41. Baang JH, Smith C, Mirabelli C, Valesano AL, Manthei DM, Bachman MA, et al. Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Replication in an immunocompromised patient. *J Infect Dis*. 2020. <https://doi.org/10.1093/infdis/jiaa666>.
 42. Clark SA, Clark LE, Pan J, Coscia A, Mckay LGA, Shankar S, et al. SARS-CoV-2 evolution in an immunocompromised host reveals shared neutralization escape mechanism. *Cell*. 2021;184(10):2605–17. <https://doi.org/10.1016/j.cell.2021.03.027>.
 43. Tarhini et al. Long-Term Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infectiousness among three immunocompromised patients: from prolonged viral shedding to SARS-CoV-2 superinfection. <https://doi.org/10.1093/infdis/jiab075>.
 44. Retrieved from: <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis> [09/16/2021].
 45. Retrieved from: <https://www.gov.br/saude/pt-br/coronavirus/vacinas/NTDoseReforo.pdf> [09/14/2021].
 46. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, Elbaz M, Neshet L, Stein M et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully-vaccinated hospitalized COVID-19 patients in Israel. *Clin Microbiol Infect*; 2021. <https://doi.org/10.1016/j.cmi.2021.06.036>
 47. Spencer AJ, McKay PF, Belij-Rammerstorfer S, et al. Heterologous vaccination regimens with self-amplifying RNA and adenoviral COVID vaccines induce robust immune responses in mice. *Nat Commun*. 2021;12:2893. <https://doi.org/10.1038/s41467-021-23173-1>.
 48. Duarte-Salles T, Prieto-Alhambra D. Heterologous vaccine regimens against COVID-19. *Lancet*. 2021;398(10295):94–5. [https://doi.org/10.1016/S0140-6736\(21\)01442-2](https://doi.org/10.1016/S0140-6736(21)01442-2).
 49. Liu X, et al. I. Com-COV Study Group. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomized, non-inferiority trial. *Lancet*. 2021. [https://doi.org/10.1016/S0140-6736\(21\)01694-9](https://doi.org/10.1016/S0140-6736(21)01694-9)
 50. Geisen UM, Berner DK, Tran F, Sümbül M, Vullriede L, Ciripoi M, et al. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. *Ann Rheum Dis*. 2021;80:1306–11.
 51. Rotondo C, Cantatore FP, Fornaro M, Colia R, Busto G, Rella V, et al. Preliminary data on post market safety profiles of COVID 19 vaccines in rheumatic diseases: assessments on various vaccines in use, different rheumatic disease subtypes, and immunosuppressive therapies: a two-centers study. *Vaccines*. 2021;9:730. <https://doi.org/10.3390/vaccines9070730>.
 52. Watad A, De Marco G, Mahajna H, Druyan A, Eltity M, Hijazi N, Haddad A, Elias M, Zisman D, Naffaa ME, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNASARS-CoV-2 vaccination. *Vaccines*. 2021;9:435. <https://doi.org/10.3390/vaccines9050435>.
 53. Retrieved from: <https://www.gov.br/saude/pt-br/coronavirus/publicacoes-tecnicas/guias-e-planos/plano-nacional-de-vacinacao-covid-19>. 16 Dec 2021.
 54. Tobaigy M, Elkout H, MacLure K. Analysis of thrombotic adverse reactions of COVID-19 AstraZeneca Vaccine Reported to EudraVigilance database. *Vaccines*. 2021;9(4):393. <https://doi.org/10.3390/vaccines9040393>.
 55. Long B, Bridwell R, Gottlieb M. Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines. *Am J Emerg Med*. 2021;49:58–61.
 56. Pishko AM, Bussel JB, Cines DB. COVID-19 vaccination and immune thrombocytopenia. *Nat Med*. 2021;27(7):1145–6.
 57. Al-Mayhani T, Saber S, Stubbs MJ, Losseff NA, Perry RJ, Simister RJ et al. Ischaemic stroke as a presenting feature of ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia. *J Neurol Neurosurg Psychiatry*, jnnp-2021–326984.
 58. Cines DB, Bussel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med*. 2021. <https://doi.org/10.1056/NEJMe2106315>.
 59. Male V. Are COVID-19 vaccines safe in pregnancy? *Nat Rev Immunol*. 2021;21:200–1. <https://doi.org/10.1038/s41577-021-00525-y>.
 60. Retrieved from: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines>. In: Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021 [09/14/2021]
 61. Dirven L, Huizinga TWJ, Allaart CF. Risk factors for reported influenza and influenza-like symptoms in patients with rheumatoid arthritis. *Scand J Rheumatol*. 2012;41(5):359–65.
 62. Durand MA, Scalia P, Elwyn G. Can shared decision making address COVID-19 vaccine hesitancy? *BMJ Evid Based Med*. 2021. <https://doi.org/10.1136/bmjebm-2021-111695>.
 63. Sanftenberg L, Kuehne F, Anraad C, et al. Assessing the impact of shared decision making processes on influenza vaccination rates in adult patients in outpatient care: a systematic review and meta-analysis. *Vaccine*. 2021;39:185–96.
 64. MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: definition, scope and determinants. *Vaccine* 2015;33:4161–4. <https://doi.org/10.1016/j.vaccine.2015.04.036>
 65. Rezende RPV, Braz AS, Guimarães MFB, Ribeiro SLE, Vieira RMRA, Bica BE, Cruz VA, Machado KLLL, Carvalho JS, Monticelo OA, Valadares LD, Baptista KL, Tavares ACFMG, Kakehasi AM, Neto ET, Melo AKG, Ferreira GA, de Souza VA, Pileggi GS, Pinheiro MM. Characteristics associated with COVID-19 vaccine hesitancy: a nationwide survey of 1000 patients with immune-mediated inflammatory diseases. *Vaccine*. 2021;39(44):6454–9.
 66. Ferreira CC, Azevedo ACC, Magalhães VP, Reis JGC, Antonelli LRV, Torres K, et al. Impact of synthetic and biological immunomodulatory therapy on the duration of 17DD yellow fever vaccine-induced immunity in rheumatoid arthritis. *Arthritis Res Ther*. 2019;21:75. <https://doi.org/10.1186/s13075-019-1854-6>.
 67. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):e44–100.
 68. Shea KM, Edelsberg J, Weycker D, Farkouh RA, Stratton DR, Pelton SI. Rates of pneumococcal disease in adults with chronic medical conditions. *Open Forum Infect Dis*. 2014;1(1). Oxford University Press.
 69. Day AL, Winthrop KL, Curtis JR. The effect of disease-modifying antirheumatic drugs on vaccine immunogenicity in adults. *Cleve Clin J Med*. 2020;87(11):695–703. <https://doi.org/10.3949/ccjm.87a.20056> (PMID: 33139263).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.