BACKGROUND

It has been shown that people with rheumatic disease (PRD) may be more susceptible to adverse outcomes from COVID-19, possibly due to the increased clustering of comorbidities among these patients.\(^1\)\(^-\)\(^3\) The Health Sciences Authority (HSA) has approved the Pfizer-BioNTech\(^\circledR\) and Moderna\(^\circledR\) COVID-19 mRNA vaccines via the Pandemic Special Access Route, and the Ministry of Health, Singapore (MOH) Expert Committee on COVID-19 Vaccination (EC19V) has published recommendations for their use.\(^4\) Other vaccines such as the Sinovac\(^\circledR\) vaccines will be evaluated at a later date.\(^5\) So far, there is evidence that both the Pfizer-BioNTech\(^\circledR\) and Moderna\(^\circledR\) vaccines are safe, immunogenic and efficacious; however, PRD on immunosuppression were excluded from both the trials.\(^6\)\(^,\)\(^7\) In this consensus recommendation, the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore (henceforth called “the Chapter”) seeks to address questions regarding the suitability of COVID-19 vaccination in PRD.

TARGET AUDIENCE

Healthcare professionals involved in the care of PRD.

METHODS

An expert panel was convened by the Chapter Chair. A core-working group reviewed the literature and formulated draft recommendations for rating by an invited task force panel, which included experts in adult and paediatric Rheumatology and Infectious Diseases. A modified Delphi approach was used. Systematic literature reviews were performed to answer four research questions (see below). Where appropriate, in lieu of a systematic review of the primary literature, international best practice guidelines and recommendations of rheumatology societies on vaccinations in PRD were reviewed. Other academic bodies’ recommendations for COVID-19 vaccination in PRD and / or immunocompromising conditions were also considered. GRADE methodology for assigning level of evidence and strength of recommendations was used.\(^8\)

GRADE system of assigning strength of recommendations:

- **Strong**: the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not.
- **Weak (conditional)**: the trade-offs are less certain - either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

PRD include, but are not limited to, those diagnosed with:

1. Chronic inflammatory arthritides (e.g. rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, juvenile idiopathic arthritis, adult onset stills disease)
2. Connective tissue diseases (e.g. systemic lupus erythematosus, immune mediated inflammatory myositis, sjögrens syndrome, systemic sclerosis)
3. Primary systemic vasculitides
4. Autoinflammatory diseases
Immunomodulatory drugs considered for this guidance include:

1. Conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) (methotrexate, sulphasalazine, leflunomide, hydroxychloroquine)
2. Biologic DMARDs (anti-tumour necrosis factor, tocilizumab, rituximab, abatacept, secukinumab, ixekizumab, anakinra, belimumab)
3. Targeted synthetic DMARDs (tofacitinib, baricitinib, upadacitinib*)
4. Immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporin A, tacrolimus)
5. Glucocorticoids (any dose)

* not included in any of the searched literature on vaccines, hence recommendation is by extrapolation

Research questions

1. Are PRD at increased risk of adverse outcomes from COVID-19?
2. Are existing approved vaccines against SARS CoV2 safe, immunogenic and efficacious in PRD?
3. Are other (non-COVID-19) recommended non-live vaccines safe, immunogenic and efficacious in PRD?
4. What is the effect of various drugs used in PRD on immunogenicity of (non-COVID-19) vaccines in PRD?

It has been shown that PRD are more susceptible to adverse outcomes from COVID-19, possibly due to the increased clustering of comorbidities among these patients.1-3 Extrapolating from guidelines for other non-live vaccines in PRD, COVID-19 vaccination is likely to be safe. In patients on immunomodulatory drugs, especially rituximab (RTX), high dose glucocorticoids (>=20mg/day of prednisolone equivalent), methotrexate, and abatacept, there may be decreased immunogenicity, and hence decreased efficacy.8-20 However, some degree of protective immunity is still likely to be achieved, other than with RTX, where immunogenicity is significantly decreased if given within 6 months of the previous dose.21-25 Antibody titres may not correlate with clinical efficacy, and the role of booster vaccination in those with insufficient antibodies has not been established. Vaccination has not been associated with flare of rheumatic disease; however, most studies were done in patients with quiescent disease. mRNA vaccines are currently untested in PRD. Of note, nucleoside modification of mRNA (for both Pfizer-BioNTech® and Moderna® mRNA vaccines) renders it unlikely to activate the innate immune response, as suggested by in vitro studies.26,27
REFERENCES


Links to other academic bodies’ guidance

1. European Alliance for Associations of Rheumatology (EULAR): https://www.eular.org/eular_sars_cov_2_vaccination_rmd_patients.cfm


**EXECUTIVE SUMMARY OF RECOMMENDATIONS**

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<thead>
<tr>
<th>Overarching principles</th>
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<td>1. Vaccination in people with rheumatic disease should be aligned with prevailing national policy.</td>
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<td>2. The decision for vaccination should be individualised, and should be explained to the patient, to provide a basis for shared decision-making between the healthcare provider and the patient.</td>
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<th>Recommendations</th>
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<tr>
<td>1. <strong>We strongly recommend</strong> that eligible patients be vaccinated against SARS-CoV2.</td>
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<td>2. <strong>We conditionally recommend</strong> that the COVID-19 vaccine be administered during quiescent disease, if possible.</td>
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<td>3. <strong>We conditionally recommend</strong> that immunomodulatory drugs, other than rituximab, can be continued alongside vaccination against SARS-CoV2.</td>
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<td>4. <strong>We conditionally recommend</strong> that the COVID-19 vaccine be administered prior to commencing rituximab, if possible. For patients on rituximab, the vaccine should be administered a minimum of 6 months after the last dose, and 4 weeks prior to the next dose of rituximab.</td>
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<td>5. <strong>We conditionally recommend</strong> that post-vaccination antibody titres against SARS-CoV2 need not be measured.</td>
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<td>6. <strong>We strongly recommend</strong> that household contacts be vaccinated against SARS-CoV2.</td>
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<td>7. <strong>We conditionally recommend</strong> that any of the approved COVID-19 vaccines may be used, with no particular preference.</td>
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# ACKNOWLEDGEMENT

## Core Working Group

<table>
<thead>
<tr>
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<th>Position and Affiliation</th>
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</table>
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## Task Force Panel

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