

Recommendations for enhanced primary series (third dose) COVID-19 vaccination for people with rheumatic diseases: chapter of Rheumatologists, College of Physicians, Singapore

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Abstract

Introduction: This review aims to provide evidence-based recommendations for an enhanced primary series (third dose) coronavirus disease 2019 (COVID-19) vaccination in people with rheumatic diseases (PRDs) in the local and regional context.

Methods: Literature reviews were performed regarding the necessity, efficacy, safety and strategies for enhanced primary series COVID-19 vaccination in PRDs. Recommendations were developed based on evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Evidence was synthesised by eight working group members, and the consensus was achieved by a Delphi method with nine members of an expert task force panel.

Results: Two graded recommendations and one ungraded position statement were developed. PRDs have impaired immunogenicity from the COVID-19 vaccine and are at an increased risk of postvaccine breakthrough severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and poor clinical outcomes, compared to the general population. We strongly recommend that PRDs on immunomodulatory drugs be offered a third dose of the messenger RNA (mRNA) vaccine as part of an enhanced primary series, after the standard two-dose regimen. We conditionally recommend that the third dose of mRNA vaccine against SARS-CoV-2 be given at least 4 weeks after the second dose or as soon as possible thereafter. There is insufficient data to inform whether the third mRNA vaccine should be homologous or heterologous in PRDs.

Conclusion: These recommendations that were developed through evidence synthesis and formal consensus process provide guidance for an enhanced primary series COVID-19 vaccination in PRDs.

Keywords: COVID-19, enhanced primary series, people with rheumatic diseases, recommendations, vaccination

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic remains a worldwide problem and threat to human life and livelihood. People with rheumatic diseases (PRDs) and/or patients on immunomodulatory drugs are at a higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and are vulnerable to poorer COVID-19 outcomes.^[1-3]

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Moreover, SARS-CoV-2 variants are more likely to arise in patients on immunosuppressive therapies.^[4] Vaccine-escape variants evolved in patients on immunosuppression are an imminent threat to public health.^[4] Therefore, it is imperative that we prevent SARS-CoV-2 infection in PRDs and/or patients with immunosuppression. An enhanced three doses primary series or a booster dose has been considered and implemented in certain countries, although controversy remains.^[5] Conversely, the risk of flare of rheumatic diseases after vaccination against SARS-CoV-2 remains unclear. Immune-mediated adverse reactions, such as myocarditis, have been reported.^[6] An additional dose of vaccine needs to be substantiated by evidence and expert consensus, especially in PRDs, to avoid compromising the confidence and acceptance of the vaccine.

We previously published recommendations for COVID-19 vaccination in PRDs.^[7] The Ministry of Health, Singapore (MOH) Expert Committee on COVID-19 Vaccination has recommended a third dose of messenger RNA (mRNA) vaccine as part of an enhanced primary series in immunocompromised patients.^[8] Herein, we aimed to summarise the evidence describing the necessity, efficacy, safety and strategies of a third dose mRNA COVID-19 vaccine in PRDs and/or patients on immunomodulatory drugs through literature review. We developed recommendations and built consensus using a Delphi method for the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore.

METHODS

We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology in developing these recommendations.^[9]

Working group

The core working group (CWG) (ML, YL, CX, AS, WF, LC, MS, SA) and the task force panel (TFP) (TA, SE, KK, AL, TL, KL, AL, AM, TT) were convened on 23 September 2021 by the Chair (ML) of the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore. The TFP comprised seven locally recognised adult rheumatologists from public and private healthcare institutions in Singapore, one paediatric rheumatologist and one infectious disease specialist. A conflict of interest declaration was signed by each member of the CWG and TFP before the consensus process.

Review question formation

The definitions of PRDs and immunomodulatory drugs considered in this recommendation are summarised in Box 1, consistent with our previous publication.^[7] In brief, we included all patients with chronic inflammatory arthritides and autoimmune connective tissue diseases and/or who are taking conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs), immunosuppressants,

Box 1. Definition of people with rheumatic diseases (PRDs) and immunomodulatory drugs.^[7]

PRDs include, but are not limited to, those diagnosed with the following:

- Chronic inflammatory arthritides (e.g., rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, juvenile idiopathic arthritis, adult-onset Still's disease)
- Connective tissue diseases (e.g., systemic lupus erythematosus, immune-mediated inflammatory myositis, Sjögren's syndrome, systemic sclerosis, overlap syndrome)
- Primary systemic vasculitides
- Autoinflammatory diseases

Immunomodulatory drugs considered for this guidance include the following:

- Conventional synthetic DMARDs (methotrexate, sulphasalazine, leflunomide, hydroxychloroquine)
- Biological DMARDs (tumour necrosis factor inhibitors, tocilizumab, rituximab, abatacept, secukinumab, ixekizumab, anakinra, belimumab)
- Targeted synthetic DMARDs (tofacitinib, baricitinib, upadacitinib)
- Immunosuppressants (cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporin A, tacrolimus)
- Glucocorticoids

Adapted from Santosa *et al.*^[7]. Immunomodulatory drugs listed above, regardless of the dosage, are administered as either monotherapy or in combination. DMARDs: disease-modifying antirheumatic drugs

biological (b) DMARDs, targeted synthetic (ts) DMARDs and glucocorticoids.

The CWG formulated the following five research questions using the Patient/Population—Intervention—Comparison/Comparator—Outcome (PICO) model to address the safety and efficacy of a third dose of mRNA COVID-19 vaccination in PRDs.^[10]

1. Do PRDs and/or patients on immunomodulatory drugs have decreased immune response to the COVID-19 mRNA vaccines compared to the general population?
2. Does a third dose of mRNA COVID-19 vaccine lead to enhanced protection of immunocompromised patients against SARS-CoV-2 infection?
3. In PRDs, are COVID-19 mRNA vaccines safe?
4. In PRDs, should the third dose be the same (homologous) or a different (heterologous) vaccine?
5. What is the best time for administration of the third dose of the vaccine?

We limited the evidence synthesis to mRNA vaccines only, as they were the approved regimen in Singapore at the time of this recommendation development.

Literature reviews

Literature reviews on the PICO questions were performed by the CWG via a literature search of published articles in PubMed. Detailed search terms and strategies are shown in the Supplemental Digital Appendix. The CWG met on 9 October 2021 to review the evidence synthesised and to formulate and finalise the recommendation statements for rating by the TFP.

Consensus of the recommendations

Members of the TFP voted anonymously on each of the recommendations using a modified Delphi approach via an online survey platform.^[11,12] Before the Delphi exercise, the TFP was provided with and required to read the summarised evidence. They were then asked to rate the level of agreement on each recommendation statement, based on the provided literature and their expertise, on a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). An agreement was defined as a score of 4 or 5. A consensus was reached if $\geq 70\%$ of TFP voted for an agreement (score 4 and 5). The CWG and TFP then convened and discussed the aggregated findings of the survey via a teleconferencing platform. Definitions were clarified and recommendation statements were rephrased, if necessary. In determining the strength of recommendations, the TFP considered the level of evidence and weighed the desirable and undesirable effects from a third dose of COVID-19 vaccination in PRDs. Recommendations were categorised as ‘strong’ when the desirable effects clearly outweighed the undesirable effects and ‘conditional’ when the desirable/undesirable effects were closely balanced. An ungraded position statement was used to reflect the general view of the TFP when there was insufficient evidence to support a graded recommendation or favour one intervention over another for a clinically important PICO question.

RESULTS

1. Evidence synthesis from literature review.

1.1. Do PRDs and/or patients on immunomodulatory drugs have decreased immune response to the COVID-19 mRNA vaccines compared to the general population?

We identified five studies addressing breakthrough infections, clinical outcomes or immunogenicity of the COVID-19 vaccine among PRDs and/or patients on immunomodulatory drugs.^[13–17] PRDs and/or patients on immunomodulatory drugs are at an increased risk of postvaccine breakthrough SARS-CoV-2 infection.^[13–15] Administrative data from a large cohort of 1,178,597 individuals in Israel have shown that the effectiveness of two doses of mRNA vaccines against SARS-CoV-2 infection was only 71% (95 confidence interval [CI]: 37%–87%) among immunosuppressed patients, in contrast to 90% (95 CI: 79%–95%) in the general population.^[13] In two multicentre observational studies, 40%–44% of hospitalised patients with breakthrough infections after vaccination were patients on immunomodulatory drugs.^[14,15]

People with rheumatic diseases and/or patients on immunomodulatory drugs have impaired immunogenicity from the vaccine, as seen by the lower rates of seroconversion compared to healthy controls.^[16,17] Following mRNA vaccination against SARS-CoV-2, the seropositivity rate and antibody levels were significantly lower among PRDs

compared to the general population (86% vs. 100%, $P < 0.0001$ and 132.9 ± 91.7 vs. 218.6 ± 82.06 binding antibody units (BAU)/mL, $P < 0.0001$, respectively).^[16] Immunogenicity measured by serum IgG antibody levels against SARS-CoV-2 spike S1/S2 proteins at 2–6 weeks after the second dose of vaccine was severely impaired by rituximab (39% seropositivity), moderately impaired by glucocorticoids (77% seropositivity), abatacept (71% seropositivity) and mycophenolate mofetil (64% seropositivity), and mildly impaired by methotrexate (92% seropositivity), compared to healthy controls (100% seropositivity).^[16] In another prospective cohort study from the Netherlands, seropositivity after the second dose of COVID-19 vaccination (either mRNA or adenovirus vector-based vaccines) was 92% in all patients with autoimmune diseases, 94% in those on methotrexate, 89% in those on methotrexate and tumour necrosis factor inhibitors, and only 43% in patients who received anti-CD20 therapies (including rituximab or ocrelizumab), compared to 95% in healthy controls. The IgG titre against the SARS-CoV-2 spike protein was about half in all patients with autoimmune diseases compared to that in healthy controls (48.6 AU/mL vs. 86.7 AU/mL).^[17] Overall, there is a low level of evidence from observational studies that consistently shows that PRDs and/or patients on immunomodulatory drugs have decreased immune response to the COVID-19 mRNA vaccines compared to the general population.

1.2. Does a third dose of mRNA COVID-19 vaccine lead to enhanced protection of immunocompromised patients against SARS-CoV-2 infection?

We identified 14 studies that evaluated whether a third dose of mRNA COVID-19 vaccine led to enhanced protection of immunocompromised patients against SARS-CoV-2 infection [Table 1], including one large observational study, one randomised controlled trial (RCT) and 12 small observational studies.^[18–31] In a general population administrative database of 1,137,804 people older than 60 years of age from Israel, the rates of confirmed infections and severe illness were lower in the booster group, where the third dose was administered at least 5 months after the standard two-dose regimen (homologous BNT162b2), than in the nonbooster group by a factor of 11.3 (95% CI: 10.4–12.3) and 19.5 (95% CI: 12.9–9.5), respectively.^[18] Despite the large effect sizes reported, we considered this observational data as low-level evidence due to indirectness (extrapolating the results from the elderly population to PRDs). In a double-blind RCT conducted among 120 organ transplant recipients, a third dose mRNA COVID-19 vaccine (Moderna) given at 2 months after the standard two-dose regimen demonstrated both enhanced humoral and T-cell responses compared to those given placebo injections.^[19] At 4 months after the third dose, detectable anti-receptor-binding antibodies were present in 33% in the intervention group compared to 18% in the placebo

Table 1. Summary of efficacy and safety of the third dose COVID-19 vaccine in people with immunocompromised status.

Study	Country	Study design	Sample size	Population	Intervention/ comparison	Time from 3 rd dose to 2 nd dose	Outcomes	Side effect (SE)
Bar-On <i>et al.</i> ^[18]	Israel	CH	1,137,804	Age ≥60 yr	Pfizer–BioNTech Booster/nonbooster	>5 months	Rate of infection and severe illness	Not reported
Del Bello <i>et al.</i> ^[24]	France	CH	396	Solid organ transplant	Pfizer–BioNTech Before/after booster	Median: 59 days IQR: 47–67 days	Augmented humoral response	No severe SE
Benotmane <i>et al.</i> ^[20]	France	CH	159	Kidney transplant	Moderna Before/after booster	Median: 51 days IQR: 48–59 days	Augmented humoral response	No severe SE
Hall <i>et al.</i> ^[19]	Canada	RCT	120	Transplant recipients	Moderna Booster/nonbooster	2 months	Augmented humoral response	No severe SE
Kamar <i>et al.</i> ^[27]	France	CH	101	Solid organ transplant	Pfizer–BioNTech Before/after booster	Mean: 60 days SD: 1 day	Augmented humoral response	No severe SE
Espi <i>et al.</i> ^[26]	France	CH	75	Dialysis	Pfizer–BioNTech Before/after booster	<3 months	Augmented humoral and cellular responses	No severe SE
Bensouna <i>et al.</i> ^[21]	France	CH	69	Dialysis	Pfizer–BioNTech Before/after booster	Median: 50 days IQR: 31–58 days	Augmented humoral response	No severe SE
Chavarot <i>et al.</i> ^[22]	France	CH	62	Kidney transplant	Pfizer–BioNTech Before/after booster	Median: 69.5 days IQR: 40–84 days	Augmented humoral response	No severe SE
Stumpf <i>et al.</i> ^[30]	Germany	CH	48	Kidney transplant	Pfizer–BioNTech Before/after booster	Mean: 68 days SD: 1 day	Augmented humoral and cellular responses	Not reported
Ducloux <i>et al.</i> ^[25]	France	CH	45	Dialysis	Pfizer–BioNTech Before/after booster	Not reported	Augmented humoral response	Not reported
Werbel <i>et al.</i> ^[31]	USA	CH	30	Solid organ transplant	Pfizer–BioNTech, Moderna, J&J Before/after booster	Median: 67 days IQR: 54–81 days	Augmented humoral response	No severe SE
Connolly <i>et al.</i> ^[23]	USA	CH	18	Autoimmune disease	Pfizer–BioNTech, Moderna, J&J Before/after booster	Median: 77 days IQR: 54–94 days	Augmented humoral response	Not reported
Longlune <i>et al.</i> ^[28]	France	CH	12	Dialysis	Pfizer–BioNTech Before/after booster	1 month	Augmented humoral response	No severe SE
Shroff <i>et al.</i> ^[29]	USA	CH	20	Solid tumour	Pfizer–BioNTech Before/after booster	Not reported	Augmented humoral response No cellular response	No severe SE

Humoral response: change of antibody titre against SARS-CoV-2; cellular response: T-cell response against SARS-CoV-2. CH: cohort studies, COVID-19: Coronavirus disease 2019, IQR: interquartile range, J&J: Johnson & Johnson, RCT: randomised controlled trial, SD: standard deviation

group (relative risk [RR] 3.1, 95% CI: 1.7–5.8, $P < 0.001$), while antibody neutralisation above the 30% threshold was seen in 60% in the intervention group compared to 25% in the placebo group (RR 2.4, 95% CI: 1.5–4.0). There were 12 and two observational studies that showed an enhanced humoral and cellular response, respectively, after a third dose of COVID-19 vaccination.^[20–31] Overall, there was a low level of evidence to show a reduction in the rates of infection and severe disease, and a low level of evidence to show increased immunogenicity, as measured by the enhanced humoral and cellular responses after a third dose of mRNA vaccine against SARS-CoV-2 in PRDs.

1.3. In PRDs, are COVID-19 mRNA vaccines safe?

Among PRDs, the rates of flares of rheumatic diseases after vaccination against SARS-CoV-2 were reported mostly from observational studies without a comparator group of patients not given vaccination. A total of 11 studies were

found.^[16,32–41] Rates of flares of rheumatic diseases after vaccination against SARS-CoV-2 from all studies ranged from 0% to 18.8%, and the rates of severe flares ranged from 0% to 1.2%.^[16,32–41] Data from the European Alliance of Associations for Rheumatology (EULAR) COVID-19 vaccination registry ($n = 1,519$) reported a 5% flare rate of the underlying rheumatic diseases, of which 1.2% were classified as severe.^[32] A prospective observational study from the USA ($n = 1,377$) showed that 11% of patients had postvaccination flares requiring treatment; there was no report of severe flare.^[33] Data from the COVID-19 Global Rheumatology Alliance vaccine survey ($n = 2,882$) reported flare of rheumatic diseases in 13.4% of patients, with 4.6% of flares requiring a new or increased dose of medications.^[34] In a multicentre observational study from Israel ($n = 686$), postvaccination disease activity remained stable in the majority of patients assessed within 6 weeks after the second dose of mRNA vaccine.^[16] Similarly, three

smaller observational studies among PRDs/patients on immunomodulatory drugs reported no postvaccination flares of the underlying rheumatic diseases.^[36,37,40] Two cohorts showed lower rates of flares in those with good control of their underlying rheumatic diseases than those with moderate or high disease activity.^[33,41] In those who flared, the majority had worsening pre-existing symptoms and non-severe flares.^[33] It is important to note that the rate of flare is variable due to differences in definitions of flare, study methodologies and background rate of flare. Additionally, most of the adverse events experienced after vaccination were mild.

From the single RCT and observational studies which evaluated efficacies of a third dose of mRNA COVID-19 vaccine [Table 1] in elderly or immunocompromised, 10 out of 14 patients reported no severe adverse events.^[19-22,24,26-29,31] Yet, among these, only one study had a nonbooster control arm.^[19] Four studies did not report on adverse events.^[18,23,25,30]

Overall, there is a very low level of evidence for harm (adverse events/risk of flare) from a third dose of mRNA vaccine in PRDs/patients on immunomodulatory drugs.

1.4. In PRDs, should the third dose be the same (homologous) or a different (heterologous) vaccine?

There are insufficient data to inform whether the third mRNA vaccine dose in PRDs should be homologous (where the third dose is the same vaccine as the initial two doses) or heterologous (where the third dose is different from the initial two doses). Hence, no graded recommendation can be proposed. One case series described 30 solid organ transplant recipients with a variety of homologous and heterologous prime-boost strategies. The various combinations led to satisfactory antibody titres in all patients who had low antibody titres after the initial two-dose strategy. Among patients who failed to mount any detectable antibody response after the initial two-dose strategy, the third dose produced detectable antibody levels in only 33% of the patients. However, no comparison between the regimens was made.^[31] Two RCTs assessed the third dose vaccination strategies in PRDs and kidney transplant patients, respectively, comparing boost strategies with an mRNA and a non-mRNA vaccine in patients who had received two homologous COVID-19 mRNA primary vaccines.^[42,43] There appeared to be no consistent advantage of one strategy over the other. All three studies reported only immunogenicity data; no clinical efficacy was reported.

1.5 What is the best time for the administration of the third dose of the vaccine?

There are no comparative studies comparing different dose intervals available in the literature. The US Centres for Disease Control and Prevention (CDC) recommends a third dose of mRNA vaccine in immunocompromised patients at least 4 weeks after the second dose.^[44] The median dosing interval

Table 2. Executive summary of recommendations.

Recommendation/statement	Level of evidence
Recommendation: We strongly recommend that PRDs on immunomodulatory drugs, who have received two doses of mRNA vaccine against SARS-CoV-2, be offered a third dose of the mRNA vaccine as part of an enhanced primary series	Low
Recommendation: For PRDs, we conditionally recommend that the third dose of mRNA vaccine against SARS-CoV-2 be given at least 4 weeks after the second dose or as soon as possible thereafter	Low
Ungraded position statement: There is insufficient data to inform whether the third mRNA vaccine should be homologous or heterologous in PRDs	Insufficient data

mRNA: messenger RNA, PRDs: people with rheumatic diseases, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

in various studies involving PRDs or transplant recipients was 30–77 days and ranged between 30 and 94 days after the second dose.^[19-24,26-28,30,31]

2. Final recommendations.

All nine members of the TFP participated in the anonymised Delphi exercise. The response rate for all statements was 100%. The executive summary of recommendations is shown in Table 2.

2.1. We strongly recommend that PRDs on immunomodulatory drugs, who have received two doses of the mRNA vaccine against SARS-CoV-2, be offered a third dose of the mRNA vaccine as part of an enhanced primary series.

Evidence has shown that PRDs have poorer outcomes with COVID-19 and an increased risk of breakthrough infection following vaccination against SARS-CoV-2. PRDs receiving a third dose mRNA vaccine against SARS-CoV-2 have reduced risk for both breakthrough and severe infections, with minimal risk of harm. The level of evidence was considered low (agreement 100%; 88.9% for 5 = strongly agree and 11.1% for 4 = agree). A strong recommendation was endorsed by 77.8% of TFP members.

2.2. For PRDs, we conditionally recommend that the third dose of mRNA vaccine against SARS-CoV-2 be given at least four weeks after the second dose, or as soon as possible thereafter.

Although there are no studies comparing different dose intervals available in the literature, the TFP agreed that the third dose of mRNA vaccine should be given at least 4 weeks after the second dose. This recommendation is consistent with the recommendations of other academic organisations.^[44,45] Given the surge in Delta variant of SARS-CoV-2, the third dose should not be delayed.

Agreement was achieved in 88.9% (11.1% for 5 = strongly agree, 77.8% for 4 = agree). A conditional recommendation was endorsed by 66.7% of TFP members.

2.3. Ungraded position statement: *There are insufficient data to inform whether the third mRNA vaccine should be homologous or heterologous in PRDs.*

There are insufficient data to inform of the comparative efficacy and safety of a homologous or heterologous vaccination regimen. The choice of the third mRNA vaccine should take into account the availability of vaccines, patient's preference and prevailing national policy.

Agreement was achieved in 100% (33.3% for 5 = strongly agree and 66.7% for 4 = agree) that either homologous or heterologous vaccine should be used in PRDs without preference.

DISCUSSION

This consensus recommendation informs healthcare providers about the necessity, efficacy, safety and strategy of the enhanced primary series (third dose) COVID-19 vaccination in PRDs based on updated literature review and evidence synthesis using the GRADE methodology. This work represents a systematic effort of the Chapter of Rheumatologists, College of Physicians, Singapore. We strongly recommend that PRDs on immunomodulatory drugs be offered a third dose of the mRNA vaccine as part of an enhanced primary series, after the standard two-dose regimen. We conditionally recommend that the third dose of mRNA vaccine against SARS-CoV-2 be given at least 4 weeks after the second dose or as soon as possible thereafter. There was insufficient data to inform whether the third mRNA vaccine should be homologous or heterologous in PRDs.

Third booster dose COVID-19 vaccinations have been implemented in many countries. However, this is distinct from a third dose COVID-19 vaccine as part of an enhanced primary series in PRDs who are vulnerable with impaired immunogenicity.^[1-3,13-17] Our consensus recommendations were developed through an updated literature review and a modified Delphi method. Fifteen adult rheumatologists, one paediatric rheumatologist and one infectious disease specialist were convened for this work, and this is representative of the healthcare providers for PRDs in Singapore. The updated evidence and consensus supported the national rollout of a third dose mRNA COVID-19 vaccine as part of an enhanced primary series in PRDs in Singapore and may facilitate discussion between patients and physicians caring for PRDs and other immunosuppressed patients (such as transplant specialists and nephrologists), from which part of the evidence is derived, in Singapore and other countries.^[19-22,24-26,28-31]

The third dose of COVID-19 vaccine as an enhanced primary series in PRDs is not only beneficial for the protection of the individual patient, but also imperative from a public health perspective to curtail persistent SARS-CoV-2 infection and potential escape mutants.^[4] The Omicron variant is currently rampant worldwide. The origin of the Omicron variant is

still elusive. SARS-CoV-2 can persist and evolve in an immunocompromised host for about 5 months.^[46] One of the plausible hypotheses is that the origin of the Omicron variant is in a South African patient with uncontrolled human immunodeficiency virus (HIV) infection,^[47] again emphasising the importance of vaccinating the immunocompromised in the public health context. Moreover, preliminary data have shown that the neutralising antibody response from the third dose of mRNA COVID-19 vaccine has enhanced cross-reactivity to the Omicron variant.^[48] This may predict similar protective effects from other new variants for PRDs and/or patients on immunomodulatory drugs.

EULAR and the American College of Rheumatology (ACR) have published the recommendations for COVID-19 vaccination in PRDs, which were updated with evolving new evidence.^[45,49,50] Both addressed wide-scoped scenarios that patients may encounter, sharing similar principles that were aligned with our previous recommendations on COVID-19 vaccination for PRDs.^[7] Our current recommendations focus on the enhanced primary series (third dose) COVID-19 vaccination in PRDs and are consistent with the EULAR and ACR recommendations with a few differences. EULAR did not specify the timing of the third dose of COVID-19 vaccination, while the ACR and our consensus recommended giving the third dose, at least 4 weeks after the second dose, which is in line with the US CDC recommendation.^[44,45,49,50] There is no unanimous consensus on which immunosuppressive or immunomodulatory drugs would affect the immune response to COVID-19 vaccination. The ACR Guidance (Version 4) recommended an additional COVID-19 vaccine dose for patients receiving any immunosuppressive or immunomodulatory therapy other than hydroxychloroquine monotherapy, without specifying the dosage.^[45] In contrast, EULAR recommended the third dose for patients receiving rituximab, abatacept, Janus kinase inhibitors, mycophenolate mofetil, cyclophosphamide, prednisolone for a prolonged period in dosage of 10 mg/day or higher and high dosage of methotrexate/azathioprine/leflunomide, with acknowledgement of the scarcity of data.^[49,50]

Limitations of this work must be considered. First, the evidence to address the efficacy, safety and strategies for the three-dose enhanced primary series COVID-19 vaccination in PRDs is scarce. Some of the evidence was extrapolated from the elderly population, patients with malignancy or transplant recipients. Second, our literature review focused on the mRNA vaccine. Therefore, the applicability of this work towards non-mRNA vaccines is limited. Third, most of the studies reported on immunogenicity rather than clinical outcomes with regards to the efficacy of a third dose COVID-19 vaccine in immunocompromised hosts.^[19-31] Lastly, we considered a list of immunosuppressants as shown in Box 1, without specifying the type, dosage and their combination. Also, we did not consider immunomodulators outside of those listed in Box 1, such as intravenous immunoglobulin, due to lack

of data. Although new data has emerged for different risks of mortality after SARS-CoV-2 infection among rheumatic diseases,^[51] no data is available for the risk of flare in relation to the type of immunosuppressant after COVID-19 vaccination at the time of our study. We are cognisant that the degree of immunosuppression is a continuum of complex state dependent on the type of rheumatic diseases, type and dose of immunosuppressants and their combination, and therefore call for shared decision-making with the attending rheumatologists and their patients.

To conclude, we have summarised the updated literature and synthesised the consensus recommendations for an enhanced primary series (third dose) COVID-19 vaccination in PRDs. Recommendations for the individual patient need to take into account the patient's clinical condition, value, preference and accessibility. These recommendations will undoubtedly evolve as new evidence becomes available.

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Conflicts of interest

Lahiri M: speakers bureau of Janssen and DKSH; consultant of Janssen and Gilead; grant/research support from Novartis; research grant from multiple pharma (Singapore National Biologics Register) and education grant from multiple pharma for Asia Pacific Rheumatology Practice Course Santosa A: speakers bureau of Amgen; consultant of Pfizer Chew LC: speakers bureau of Pfizer and Abbvie; consultant of Pfizer; research support from Abbvie Fong W: speakers bureau of Abbvie, DKSH, GSK and Novartis Lee TH: speakers bureau of Sanofi Low A: speakers bureau of Boehringer Ingelheim; consultant of Boehringer Ingelheim and Johnson & Johnson Leung YY: speakers bureau of Abbvie, DKSH, Janssen, Novartis and Pfizer; SMJ editorial board member who was not involved in the review and publication decision of this paper.

Supplemental digital content

Appendix at <http://links.lww.com/SGMJ/A241>

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APPENDIX

Literature search was done in PubMed by researchers from the core working group.

Questions	Researchers	Search date	Search strategy using PubMed	Study selection
1. Do PRD and/or patients on immunomodulatory drugs have decreased immune response to the COVID-19 mRNA vaccines compared to the general population?	LC, MS	19 th Sept 2021	- MeSH terms: (vaccine OR vaccination OR active immunisation) AND (autoimmune disease OR rheumatology OR host, immunocompromised OR immunocompromised host OR immunocompromised patient) - Filters: Full text, Clinical Trial Protocol, Consensus Development Conference, Consensus Development Conference, National Institutes of Health, Guideline, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Systematic Review, in the last 5 years, Humans, English - Additional citations were added from the manual search.	181 returns - 180 excluded (irrelevant 179, review/commentary 1) - 4 added from cross reference check Final inclusion: 5 studies
2. Does the third dose of mRNA COVID-19 vaccine lead to enhanced protection of immunocompromised patients against COVID-19 infection?	CX, YL	21 st Sept 2021	- keywords (COVID-19 OR SARS-COV-2) AND (vaccine OR vaccination) AND ("third dose" OR "three doses") - The following articles were also excluded: review articles, commentary, those reporting unrelated topics. - Additional citations were added from the manual search.	40 returns - 33 excluded (irrelevant 28, inactivated vaccine 2, adenovirus vaccine 1, review/commentary 2) - 7 added from cross reference check Final inclusion: 14 studies
3. In PRD, are COVID-19 mRNA vaccines safe?	SA, WF	7 th Oct 2021	((COVID-19[MeSH Major Topic]) OR (SARS-CoV-2[MeSH Major Topic])) AND ((vaccine[MeSH Major Topic]) OR (vaccination[MeSH Major Topic])) AND ((rheumatic disease[MeSH Terms]) OR (rheumatism[MeSH Terms]) OR (autoimmune disease[MeSH Terms]) OR (immunocompromised[MeSH Terms]) OR (immunocompromised host[MeSH Terms]) OR (immunocompromised	136 returns - 125 excluded (irrelevant 124, inactivated vaccine 1) Final inclusion: 11 studies

			patient[MeSH Terms])) • Additional citations were added from the manual search.	
4. In PRD, should the third dose be the same (homologous) or a different (heterologous) vaccine?	AS	9 th Oct 2021	• (((covid 19 OR sars cov 2[MeSH Major Topic]) AND (vaccination OR vaccine[MeSH Major Topic])) AND (booster OR third)) AND (immunocompromised OR immunosuppressed OR immunocompromised OR transplant OR chemotherapy OR rheumatic) • Additional citations were added from the manual search.	163 returns - 160 excluded (irrelevant) Final inclusion: 3 studies
5. What is the best time for the administration of the third dose of the vaccine?	ML	9 th Oct 2021	1."covid 19"[MeSH Major Topic] OR "sars cov 2"[MeSH Major Topic] 2."vaccination"[MeSH Major Topic] OR "vaccines"[MeSH Major Topic] 3.booster[Title/Abstract] OR ("3rd"[All Fields] AND "dose"[All Fields]) OR (("third"[All Fields] OR "thirds"[All Fields]) AND "dose"[All Fields]) 4."immunocompromisation"[All Fields] OR "immunocompromise"[All Fields] OR "immunocompromised host"[MeSH Terms] OR ("immunocompromised"[All Fields] AND "host"[All Fields]) OR "immunocompromised host"[All Fields] OR "immunocompromised"[All Fields] OR "immunocompromising"[All Fields] OR "transplantability"[All Fields] OR "transplantable"[All Fields] OR "transplanted"[All Fields] OR "transplantating"[All Fields] OR "transplantation"[MeSH Terms] OR "transplantation"[All Fields] OR "transplantations"[All Fields] OR "transplanted"[All Fields]	253 returns - 249 excluded (irrelevant) - 2 added from cross reference check Final inclusion: 6 studies

			OR "transplanting"[All Fields] OR "transplantation"[MeSH Subheading] OR "transplantation s"[All Fields] OR "transplanter"[All Fields] OR "transplanters"[All Fields] OR "transplantation"[All Fields] OR "transplants"[MeSH Terms] OR "transplants"[All Fields] OR "transplant"[All Fields] OR "rheumatic diseases"[MeSH Terms] OR ("rheumatic"[All Fields] AND "diseases"[All Fields]) OR "rheumatic diseases"[All Fields] OR "rheumatics"[All Fields] OR "rheumatism"[All Fields] OR "rheumatic"[All Fields] OR "rheumatisms"[All Fields] #1 AND #2 AND #3: 64 results #1 AND #2 AND #4: 201 results #1 AND #2 AND #3 AND #4: 12 results • Additional citations were added from the manual search.	
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