PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Immunogenicity and safety of mixed COVID-19 vaccine regimens in patients with immune mediated inflammatory diseases: a single-centre prospective cohort study
AUTHORS	Hitchon, Carol; Mesa, Christine; Bernstein, Charles; Marrie, Ruth Ann; Card, Catherine; O'Brien, Sheila F; Kim, John

VERSION 1 – REVIEW

REVIEWER	Eviatar, Tali Tel Aviv University, Rheumatology
REVIEW RETURNED	13-Feb-2023

GENERAL COMMENTS	This is a single center prospective study that compared homologous to heterologous anti-SARS-CoV-2 vaccine regimens in IMID patients receiving various immunomodulators. The number of participants is considerable, specimen collection and a large amount of data was collected. I think that the topic is justifiable, although some revisions should be made. - As I understand, the primary objective was to assess the effect of different vaccine regimens on the immunogenicity to two different SARS-CoV-2 antibodies. - The aim of the study is not clearly defined in the methods section. I suggest also to define secondary objectives (kinetics of seropositivity or titers over time/vaccine doses, comparison of immunogenicity between the different groups - IA, SARD, etc., effect of the regimens on actual COVID-19 infection (efficacy), and of course safety of the different regimens (disease activity). - Were the "healthy" controls matched for hetero/homo vaccine regimen? This should also be stated in the manuscript. If not - the regimens that these controls received should be stated. - The justification to use two anti SARS antibodies to assess the response to the vaccine is not clear from the manuscript. Most studies use one of them (anti spike or anti RBD), and to the best of my knowledge they are interchangeable. Why did the authors choose to use both? And if both are used - why not to define "seropositivity" as both spike+RBD positive? Why not to do the multivariable analysis regarding this definition of seropositivity? - There is little data regarding the waning of antibodies after vaccine doses. This study has data of antibody titers 3 months post doses which is scarce in the literature of AIIRD patients. Do specific treatments affect the decline of antibodies? Some data in the literature suggests that TNFi cause more rapid antibody declines. Do the antibodies decline faster for certain disease groups? and most important - Do different vaccine regimens have different titer kinetics?

	- COVID-19 infections were recorded during the study. I suggest to include an analysis of the association of hetero/homologous regimens and also antibody titers/seropositivity and different medication class with COVID-19. An analysis of the time of infection since last vaccine may also serve to inform booster timings. - The grouping of medication needs refinement: first of all - it is not clear from the Methods what medications each group consists of. Second - the effect of different biologics on immunogenicity differs substantially - anti cytokine biologics appear to effect antibody titers and also infection much less than anti-cellular (B-cell and T-cell targeted therapies) medications. Third - if some SARD patients were treated only with hydroxychloroquine - in what group were they considered? HCQ does not hamper immune responses. - I suggest to add the number of patients treated with each medication in the supp table 1. I suggest to group all systemic steroids together and to include the mean/median prednisone equivalent dose in each group in the text, and maybe in the analyses (of the primary outcome and maybe some of the secondary outcomes). Where actual patients treated with penicillamine and auranofin? How many patients were treated with cyclophosphamide? Grouping can be also done according to medications used - for example - steroids as I suggested before and also anti TNF (IBD and IA), and B-cell depletion (IA, SARD and MS patients), etc. - in page 19, lines 13-14 there is a comparison of anti NC and anti S/RBD titers. I am not sure of the conclusions that can be drawn from such a comparison. The titers of different antibodies are not necessarily matching. What is the meaning of this comparison? - I think that all diagnoses included in each group should be clearly stated in the results section (for IA - how many SPA, PSA, etc., for SARD - myositis, scleroderma, etc, for IBD - UC and Crohn's...) - in the strengths of the study is says that "systematic collection of data on COVID-19 infection..." while the data on infections relied on participants recall only (or am I wrong? Were PCR/antigen test results confirmed? If so - it is not clear). - minor revisions: The headings of tables are not sufficiently elaborated. For example - table 3 is the results of the multivariable analysis. It is not clear from the heading. In table 3 - RA should be IA. In line 9 of the abstract there's a redundant "vaccine" Thank you very much for the effort done in conducting this study,

REVIEWER	Jacobs, Jeremy W Yale School of Medicine
REVIEW RETURNED	24-Feb-2023

GENERAL COMMENTS	Hitchon et al. analyze the immunogenicity and safety of COVID-19 vaccine regimens in the context of immune mediated inflammatory diseases in a single-institution cohort. This is a well-written manuscript discussing the details of not only vaccine effectiveness, but the potential for adverse immunologic events in a patient population in whom various reports have suggested may be at an increased risk for autoimmune conditions and/or flares. I have a few suggestions to strengthen this already excellent manuscript. 1. Results: Page 13, lines 9-11

	Based on the findings that flare rate post V1 was not significant, but it was for V2, V3, V4, and any vaccine - could you comment on the potential for recall and reporting bias due to reports of increased autoimmune reactions? While I believe the data, there is potential that as increased reports of individuals with IMIDs experiencing disease flares following vaccination, this may have influenced the population in this study. 2. Similarly, were patients with known severe, active autoimmune disease offered vaccines? While this data may not be available, I ask because from anecdotal experience, numerous institutions began suggesting that individuals with active autoimmune symptoms or autoimmune flares postpone their vaccines, particularly following reports of worsened symptoms in the literature. 3. Did any patients receive monoclonal antibody therapy or convalescent plasma? This could have affected titers and/or results. 4. Results: Page 18, lines 32-33: Please state the number of participants (in addition to the percentage) where you say "…whereas 34.6% of participants reported mild symptoms consistent with COVID-19…"

REVIEWER	Velikova, Tsvetelina Sofia University St Kliment Ohridski, Medical Faculty
REVIEW RETURNED	28-Feb-2023

GENERAL COMMENTS	Specific comments on weaknesses of the article and what could be improved: Major points - none Minor points 1. Key message - 1st question - "Some treatments" might be referred to immunosuppressant treatment 2. Could you please discuss the clinical implications of the results, what recommendations would you give

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Tali Eviatar, Tel Aviv University
Comments to the Author:
Dear authors,
This is a single center prospective study that compared homologous to heterologous anti-SARS-CoV-2 vaccine regimens in IMID patients receiving various immunomodulators. The number of participants is considerable, specimen collection and a large amount of data was collected.

I think that the topic is justifiable, although some revisions should be made.

We thank Reviewer 1 for their thoughtful review and constructive suggestions. Please find our response to each comment below:

- As I understand, the primary objective was to assess the effect of different vaccine regimens on the immunogenicity to two different SARS-CoV-2 antibodies.

> Yes, the primary objective of this report was to assess post vaccine humoral immunogenicity comparing vaccine combinations. We have stated the primary and secondary objectives in the methods section.

- The aim of the study is not clearly defined in the methods section. I suggest also to define secondary objectives (kinetics of seropositivity or titers over time/vaccine doses, comparison of immunogenicity between the different groups - IA, SARD, etc., effect of the regimens on actual COVID-19 infection (efficacy), and of course safety of the different regimens (disease activity).

> We have added the following to the methods section:
> "Study Objectives: The primary study objective was to compare post-vaccination anti-spike, -receptor binding domain (RBD) and -nucleocapsid (NC) IgG antibody seroconversion and titres across vaccine regimens. Secondary study objectives were to determine the kinetics of seropositivity and titers over across vaccine doses, to compare immunogenicity across IMIDs, to determine the effect of vaccination on COVID-19 infection (efficacy), and to determine post vaccine IMID disease activity/state and self-reported IMID flare (safety)."

- Were the "healthy" controls matched for hetero/homo vaccine regimen? This should also be stated in the manuscript. If not - the regimens that these controls received should be stated.

> We were not able to match the controls by vaccine regimen as these data were not collected by Canadian Blood Services, the source of the control samples. This has been stated.

- The justification to use two anti SARS antibodies to assess the response to the vaccine is not clear from the manuscript. Most studies use one of them (anti spike or anti RBD), and to the best of my knowledge they are interchangeable. Why did the authors choose to use both? And if both are used - why not to define "seropositivity" as both spike+RBD positive? Why not to do the multivariable analysis regarding this definition of seropositivity?

> We tested both anti-RBD and anti-Spike as these measure potentially different anti-viral targets. Anti-RBD antibodies are specific to the RBD domain – located in S1 region of the spike protein and that is the site that binds ACE on host cells. Anti-Spike antibodies may target other parts of the Spike protein.
>
> We measured both for several reasons.
>
> 1. As the reviewer indicated, there is some variability across studies regarding reporting anti-S and/or anti-RBD. Our control samples only had anti-S tested. As it was feasible to test both, and to help comparisons with other reports, we tested both. As we showed in Table 2, the concordance of anti-S and anti-RBD seropositivity was lower after the first vaccine (52% anti-S1 +ve vs 58.9% anti-RBD +ve) . When we compared seroconversion rates using combined seropositivity (anti-S and/or anti-RBD), results of the multivariate analysis were similar.
>
>   We added a statement to this effect in the results " Participants over age 65 years, diagnosed with MS, or taking biologics, were less likely to seroconvert by the second vaccine in multivariable models. Results were similar if seroconversion was defined as seropositivity to anti-RBD and/or anti-Spike (Table 3)."

2. Data from Feng et al (38) suggested that titers needed to achieve 80% vaccine efficacy for the alpha variant were higher for (binding) anti-RBD than for (binding) anti-Spike suggesting these antibodies may reflect differences in vaccine protective immunity.

   We added a statement to this effect to the discussion " Antibody binding titers have been shown to correlate with neutralizing and cellular responses which in turn correlate with vaccine efficacy, although the titers needed to achieve good vaccine efficacy may differ for anti-Spike and anti-RBD [38]"

   38. Feng, S., Phillips, D.J., White, T. *et al.* Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* **27**, 2032–2040 (2021). https://doi.org/10.1038/s41591-021-01540-1

- There is little data regarding the waning of antibodies after vaccine doses. This study has data of antibody titers 3 months post doses which is scarce in the literature of AIIRD patients. Do specific treatments affect the decline of antibodies? Some data in the literature suggests that TNFi cause more rapid antibody declines. Do the antibodies decline faster for certain disease groups? and most important - Do different vaccine regimens have different titer kinetics?

We agree these are all very important questions! We acknowledge other work that has shown the impact of anti-TNFs (used for RA and IBD) on vaccine mediated immunogenicity. We have looked closer into our data and report the following:

In paired analysis we saw differences in the degree of waning (ie change in titer between 1mo post V2 and 3 months post V2) for anti -RBD and anti-S1 across IMIDs with generally greater waning for IBD and MS than for IA and SARDs.

Treatment affected post vaccine seroconversion finding less seroconversion with use of biologics and immunosuppressants. (we showed this in the multivariable models shown in Table 3). Treatment also affected titers with lower titers achieved in patients on biologics and immunosuppressive medication compared to individuals on immunomodulators or no therapy. While there were differences in the magnitude of titer change across treatment groups, this appeared mainly due to comparisons with immunomodulators which had greater waning possibly because this group had higher titers immediately post vaccine. (see figure)

We were not powered to test differences between biologics however we describe differences between anti-TNF, B cell depleting therapy and all other biologics across vaccine regimens. We show this in the new supplemental figure and in the new supplemental table. There were subtle differences in waning for individuals receiving homologous mRNA vs mixed vector/mRNA of the same type for anti-RBD or anti-S1.

We have added the following to the results section:

"In paired analysis the decline in titers between 1mo post V2 and 3 mo post V2 for anti-S1 and anti-RBD differed across vaccine mixture (anti-RBD p=0.026; anti-S1 p=0.02) however this was mainly due to minimal titer changes for individuals receiving homologous vector vaccines who also had lower titers overall. We observed greater titer change between those that received vector/mRNA versus mRNA/mRNA combinations for anti-S1, but did not see differences in anti-RBD titer change between those that received vector/mRNA versus mRNA/mRNA combinations. [median (IQR) anti-S1 vector/mRNA 1591.6 (3002.7) vs

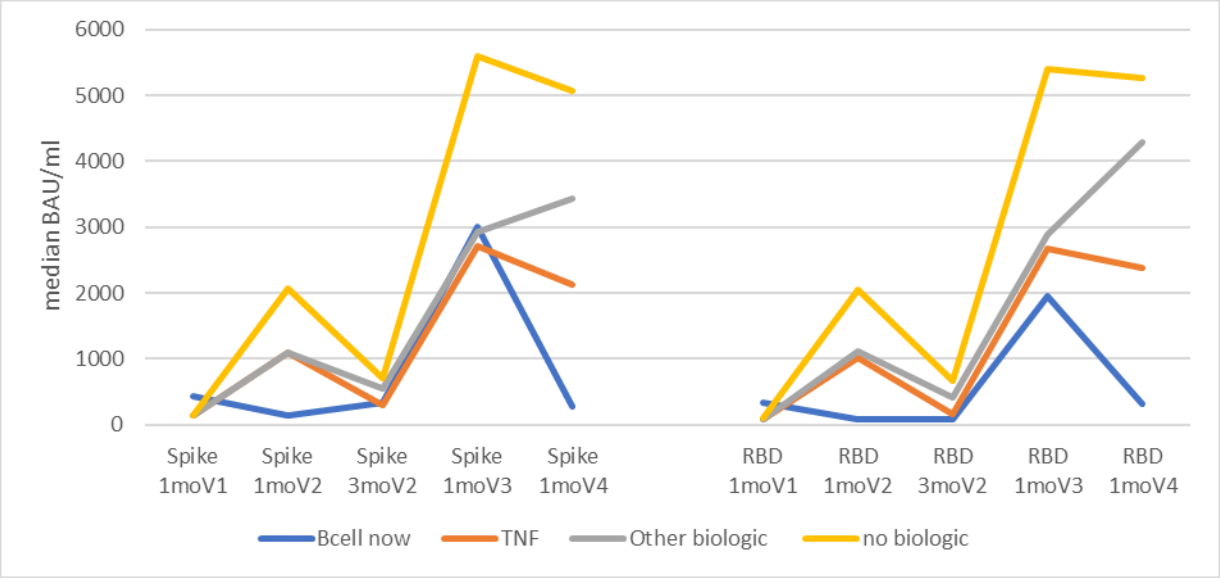
homologous mRNA 1086.3 (1608.8) p=0.021; anti-RBD vector/mRNA 1469.9 (2086.5) vs 1124.5 (1402.4) p=0.051]. For individuals receiving homologous mRNA (BNT/BNT vs mRNA1273/mRNA1273) there was no difference in waning for anti-RBD or anti-S1. [anti-RBD titer change: BNT/BNT 1080.6 (2405) vs mRNA1273/mRNA1273 1434.9 (2465.1) p=0.58; anti-S1 titer change BNT/BNT 1051.9 (1674.1) vs mRNA1273/mRNA1273 1567.5 (2481.9) p=0.39]. There was no difference in waning for individuals receiving homologous mRNA vs mixed vector/mRNA of the same mRNA type for anti-RBD or anti-S1. There was no difference in titer change across different biologic categories (anti-TNF versus Bell depletion versus other biologic; anti-RBD p= 0.30; anti-S1 p=0.14) (Supplemental Figure 4).

The following was added to the discussion section:

"Our observations in IMIDs confirm that second, and at least third vaccination courses are needed to generate acceptable humoral immunogenicity, that mRNA vaccines can overcome limited responses to vector vaccines, and that the type of mRNA administered has minimal impact on waning vaccine titers following the second vaccination."

"We were not able to confirm prior reports of the impact of different biologic categories on vaccine titers however our study was not powered for this question. Additional studies are needed to evaluate if there are important differences across mRNA vaccines and vaccine intervals for optimal protection against variants of concern to inform recommendations for additional vaccinations in IMIDs. "

Supplementary Figure 4 Median titers of anti-Spike and anti-RBD for individuals on different biologic categories



Supplementary Table Titers of anti-Spike and anti-Receptor Binding Domain IgG based on use of biologic at each visit

(values are medians (IQR)

	B cell targeting now	anti-TNF	other biologic	no biologic	B cell targeting past
Spike 1moV1	443	151	137	144	120
Spike 1moV2	137	1100	1089	2062	1884
Spike 3moV2	330	289	560	701	316
Spike 1moV3	3011	2710	2929	5600	12938
Spike 1moV4	278	2128	3427	5060	11221
RBD 1moV1	331	89	80	107	81
RBD 1moV2	81	1027	1121	2054	1133
RBD 3moV2	94	157	420	676	286
RBD 1moV3	1959	2664	2886	5405	13673
RBD 1moV4	320	2376	4285	5270	12236
N 1moV1	2	14	8	77	2
N 1moV2	5	37	16	152	4
N 3moV2	5	34	20	154	5
N 1moV3	8	34	19	140	5
N 1moV4	5	18	11	46	5

RBD= receptor binding domain ; N=number of participants on each medication type at the visit; TNF= Tumor Necrosis Factor; B cell depletion = rituximab, belimumab or ocrelizumab

- COVID-19 infections were recorded during the study. I suggest to include an analysis of the association of hetero/homologous regimens and also antibody titers/seropositivity and different medication class with COVID-19. An analysis of the time of infection since last vaccine may also serve to inform booster timings.

The number of infections in the study is low and therefore this makes testing the associations of IMID treatment, vaccine mixture and anti-RBD/antiS1 titers with future infection / anti-NC positivity difficult. We did not see a difference in the type /category of IMID treatment between anti-NC positive versus negative individuals. We have now reported the medications used in the results section. We have added the number of anti-NC positive participants at each visit to Supplementary figure 6. We have added a supplemental table that documents the characteristics of the participants who were anti-NC seropositive. Some participants were asymptomatic thus this data is not available. The numbers of infections at each time point are too low to compare titers of RBD and S (for the preceeding visit) between those that were later seropositive or seronegative. Details on the time of infection are lacking for individuals who were asymptomatic.

The results section has been modified as below:

"Twenty-five patients were seropositive for anti-NC antibodies on at least one visit (8 IA, 8 SARDs, 3 MS, 6 IBD) and for 4 of these individuals, seropositivity persisted with declining titers across consecutive visits spanning 3 to 6 months. All but one MS participant were also anti-RBD and anti-S1 seropositive. ~~The anti-NC titers obtained closest to COVID-19 infection~~

~~(i.e. the first positive sample) were lower than anti-S1 or anti-RBD titers at the same visit [median titer (25% and 75% quartile) BAU/ml first positive test anti-NC 28.5 (18.0, 62.2); anti-S1 12443.1 (7027.5, 27143.0); anti-RBD 13851.5 (6244.87, 35743.5) p<0.001 for both anti-S1 and anti RBD] and across all visits [median (25% and 75% quartile) BAU/ml anti-S1 1416.3 (470.9, 4090.6) anti-RBD 1230.1 (284.4, 3747.3) p<0.001 for both anti-S1 and anti-RBD]~~. Anti-RBD and anti-S1 titers were higher in anti-NC positive compared to anti-NC negative samples [median (range; IQR) anti-RBD 11755.3 (20373.1) vs 1248.0(27-78936.2; 53278.7); anti-Spike 11254.4 (77.3-68157.0; 15352.6) vs 1313.1 (37.4-87401.3; 3106.6)]. Nine of these 25 anti-C seropositive individuals were asymptomatic, 10 were taking biologics (4 anti-TNFs, 3 current or past B cell targeting therapies, 5 other biologics), 6 immunosuppressives (5 methotrexate, 2 azathioprine, 1 mycophenolate), 8 immunomodulating agents and one MS participant was on no IMID medication. Although the rates of anti-NC positivity increased over the course of the study, anti-NC titers did not vary by vaccine status status (heterologous or homologous) nor by date tested (Table 2, Supplementary Table X Supplementary Figure 6)."

- The grouping of medication needs refinement: first of all - it is not clear from the Methods what medications each group consists of. Second - the effect of different biologics on immunogenicity differs substantially - anti cytokine biologics appear to effect antibody titers and also infection much less than anti-cellular (B-cell and T-cell targeted therapies) medications. Third - if some SARD patients were treated only with hydroxychloroquine - in what group were they considered? HCQ does not hamper immune responses.

- I suggest to add the number of patients treated with each medication in the supp table 1.
I suggest to group all systemic steroids together and to include the mean/median prednisone equivalent dose in each group in the text, and maybe in the analyses (of the primary outcome and maybe some of the secondary outcomes).

See below

Where actual patients treated with penicillamine and auranofin? How many patients were treated with cyclophosphamide?

See below

Grouping can be also done according to medications used - for example - steroids as I suggested before and also anti TNF (IBD and IA), and B-cell depletion (IA, SARD and MS patients), etc.

We grouped the medication in categories according to the degree of presumed immunosuppression per expert opinion and consistent with what we have used for different studies on these IMIDs. Hydroxychloroquine was considered an immunomodulator. The supplemental table defines what medication is included in each group and for each IMID as there is not room to include all medications for each IMID in the methods section. As the grouping was done prior to study start, we listed all medication used for each condition. No patients were receiving penicillamine, auranofin or cyclophosphamide during the study (but some had had taken these agents in the past). Since some individuals were on combination therapy we assigned the most immunosuppressive category (ie anti-TNF and methotrexate would be categorized as anti-TNF/biologic). We added the number of individuals taking each category to the supplemental table. In the methods we list the more common agents used for each category/group. In Table 1 we listed the biologics taken. In Supplemental Table 1 we indicate the number of participants

We have analyzed vaccine responses based on these subcategories of biologics. (as above). We changed the methods section to reflect the categories in supplemental table 1.

". IMID treatment was subcategorized as anti-inflammatories and immunomodulators such as 5-ASA sulfasalazine, hydroxychloroquine ,glatiramer, and interferon therapy, traditional immunosuppressants such as methotrexate, leflunomide, azathioprine, and mycophenolate, biologic or advanced therapies such as anti-tumor necrosis factor agents, B cell depleting agents, vedolizumab, fingolimod, anti-cytokine therapies, other biologics and janus kinase inhibitors, and corticosteroids (Supplementary Table 1). "

- in page 19, lines 13-14 there is a comparison of anti NC and anti S/RBD titers. I am not sure of the conclusions that can be drawn from such a comparison. The titers of different antibodies are not necessarily matching. What is the meaning of this comparison?

This has been removed

- I think that all diagnoses included in each group should be clearly stated in the results section (for IA - how many SPA, PSA, etc., for SARD - myositis, scleroderma, etc, for IBD - UC and Crohn's...)

This has been added as a footnote to Table 1

- in the strengths of the study is says that "systematic collection of data on COVID-19 infection..." while the data on infections relied on participants recall only (or am I wrong? Were PCR/antigen test results confirmed? If so - it is not clear).

Subjects were asked at each visit if they had new confirmed COVID-19 (and reported if this was based on PCR or rapid antigen detection tests and the date of testing), mild viral symptoms without testing / suspected COVID-19 infection, or no infection symptoms. PCR testing was restricted in our region after Dec 2021 and tests after that time were mainly home administered rapid antigen tests. Medical record reviews would only capture PCR testing. We have modified the methods section to state:

"participant reported interval COVID-19 infections with type of confirmatory test…",

- minor revisions: The headings of tables are not sufficiently elaborated. For example - table 3 is the results of the multivariable analysis. It is not clear from the heading.

The heading for Table 3 has been changed to " Clinical variables associated with seroconverstion one month following second vaccine RBD=Receptor binding domain; S1 = Spike protein; Ref = reference category; NA = not able to compute

In table 3 - RA should be IA. This change has been made
In line 9 of the abstract there's a redundant "vaccine" This change has been made

Thank you very much for the effort done in conducting this study,
Thank you!

Reviewer: 2
Dr. Jeremy W Jacobs, Yale School of Medicine
Comments to the Author:
Hitchon et al. analyze the immunogenicity and safety of COVID-19 vaccine regimens in the context of immune mediated inflammatory diseases in a single-institution cohort. This is a well-written manuscript discussing the details of not only vaccine effectiveness, but the potential for adverse immunologic events in a patient population in whom various reports have suggested may be at an increased risk for autoimmune conditions and/or flares.

I have a few suggestions to strengthen this already excellent manuscript.
We thank the reviewer for their review. Please find our responses to each comment below

1. Results: Page 13, lines 9-11
Based on the findings that flare rate post V1 was not significant, but it was for V2, V3, V4, and any vaccine - could you comment on the potential for recall and reporting bias due to reports of increased autoimmune reactions? While I believe the data, there is potential that as increased reports of individuals with IMIDs experiencing disease flares following vaccination, this may have influenced the population in this study.

> The disease activity/state data was collected 1 month post each vaccine using the validated questionnaires. These questionnaires include a question on self reported flare which was used to report flare rates. The attribution of flare to vaccine or other factors is not known.

2. Similarly, were patients with known severe, active autoimmune disease offered vaccines? While this data may not be available, I ask because from anecdotal experience, numerous institutions began suggesting that individuals with active autoimmune symptoms or autoimmune flares postpone their vaccines, particularly following reports of worsened symptoms in the literature.

> We can only comment on the disease activity of the individuals entering our study who would have been offered (and accepted) COVID vaccination. In our region, initial access to COVID-19 vaccines was restricted for individuals with autoimmune conditions or on immunosuppressive medication (but there was no clause for disease severity/activity).

3. Did any patients receive monoclonal antibody therapy or convalescent plasma? This could have affected titers and/or results.

> At the time of the study, these treatments were not widely available except for severe COVID-19 infection. We are collecting data on the use of Paxlovid, and convalescent serum.

Results: Page 18, lines 32-33: Please state the number of participants (in addition to the percentage) where you say "…whereas 34.6% of participants reported mild symptoms consistent with COVID-19…"
This has been added

Reviewer: 3
Dr. Tsvetelina Velikova, Sofia University St Kliment Ohridski
Comments to the Author:

We thank the reviewer for their suggestions.

Specific comments on weaknesses of the article and what could be improved:
Major points - none

Minor points

1. Key message - 1st question - "Some treatments" might be referred to immunosuppressant treatment

We have removed this section at the request of the editors

2. Could you please discuss the clinical implications of the results, what recommendations would you give

In our conclusions we state ". At least two doses that include a mRNA vaccine, either homologous or mixed vaccine types are needed to generate humoral immunity comparable to the general population. The observed decline in humoral responses support the use of third and subsequent vaccine doses for IMIDs."

Based on our results, these are the recommendations best supported by the data.

*** ***

COI statements:

Reviewer: 1
Competing interests of Reviewer: None.

Reviewer: 2
Competing interests of Reviewer: None.

Reviewer: 3
Competing interests of Reviewer: None.

VERSION 2 – REVIEW

REVIEWER	Eviatar, Tali Tel Aviv University, Rheumatology
REVIEW RETURNED	18-Apr-2023

GENERAL COMMENTS	Thank you again for revising the manuscript, and adding interesting and importand data. I have only very minor corrections: "apremelast" should be changed to "apremilast". "kineret" is the brand name of "anakinra". "b-cell depleting" may be changed to "b-cell targeted therapies" if belimumab is included in this group. "vaccine titers" should be changed to "antibody titers" (or "humoral response"/"immunogenicity"). In some sentenced it says "RBD titers" and "S1 titers" - this should be "anti-RBD/anti S1".

REVIEWER	Jacobs, Jeremy W Yale School of Medicine
REVIEW RETURNED	20-Apr-2023

GENERAL COMMENTS	The authors have adequately addressed all of my initial concerns. I thank them for this important contribution to the literature.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Tali Eviatar, Tel Aviv University

Comments to the Author:

Thank you again for revising the manuscript, and adding interesting and importand data.

I have only very minor corrections: "apremelast" should be changed to "apremilast". "kineret" is the brand name of "anakinra". "b-cell depleting" may be changed to "b-cell targeted therapies" if belimumab is included in this group.

"vaccine titers" should be changed to "antibody titers" (or "humoral response"/"immunogenicity").

In some sentenced it says "RBD titers" and "S1 titers" - this should be "anti-RBD/anti S1".

These changes have been made. We analyzed RBD and S1 titers separately except where indicated thus did not change the reporting to avoid confusion.

Reviewer: 2

Dr. Jeremy W Jacobs, Yale School of Medicine

Comments to the Author:

The authors have adequately addressed all of my initial concerns. I thank them for this important contribution to the literature.

Thank you.