

## **Clinically confirmed long post-COVID vaccination syndrome should be taken seriously**

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Handling editor:

Michal Heger

Department of Pharmaceutics, Utrecht University, the Netherlands

Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

Review timeline:

Received: 17 August, 2022  
Editorial decision: 12 September, 2022  
Revision received: 13 September, 2022  
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1<sup>st</sup> Editorial decision  
12-Sep-2022

Ref.: Ms. No. JCTRes-D-22-00120

Take long post-COVID vaccination syndrome seriously  
Journal of Clinical and Translational Research

Dear Dr. Finsterer,

Reviewers have now commented on your paper. Reviewer # 1 is opposed to the publication, while reviewer # 2 recommended a major revision. We have studied the reviewers' comments, and we are unequivocally siding with the reviewers' opinion, particularly reviewer # 1. Nonetheless, we do feel that the comments do not block the possibility that your paper is eventually publishable. In order to achieve this, we are asking the authors to exercise more rigor in corroborating the conclusions and adopting a more critical stance towards their data, which essentially embodies the opinion of the first reviewer. Please take into account the entire available body of evidence when formulating your arguments and tone done your position there where it is warranted in the ake of weaker evidence. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each

point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Oct 12, 2022.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The authors describe 5 patients with so-called long-post COVID vaccination syndrome following an anti-SARS-CoV-2 vaccination. All patients had a variety of symptoms that lasted longer than 6 months.

I share the authors' opinion that side effects after COVID19 vaccinations exist and patients with them should be taken seriously. For example, patients occasionally report long-lasting fatigue. I also agree that this is an important issue about which we do not yet have sufficient knowledge

Unfortunately, there are some difficulties in this manuscript. From my point of view, it can not be published in this form.

1. The authors introduce the paper by defining the LPCVS and explicitly point out that there are no or only mild findings in clinical or instrumental investigations for this syndrome. However, this definition does not apply to all patients described, since diagnostics to rule out organic causes have not (yet) been carried out or are not described in the manuscript. For example, the MRI is still pending for patient 1 and for patient 4 with facial paralysis no diagnostics are described at all (e.g. exclusion of other viral diseases, cranial imaging, etc.).

2. I understand that it is of course difficult to prove that symptoms are due to a vaccination, since there is usually no specific diagnosis for causality. Nevertheless, diagnostics should at least be carried out to rule out other causes of the symptoms. Otherwise, it is not correct to attribute symptoms to a vaccination just because there is a temporal association (which does not yet prove a causality). In the case of the fourth patient in particular, I find it critical to attribute the symptoms to the vaccination, since a SARS-CoV-2 infection was detected at the same time and, as described above, no further diagnostics were carried out. The authors also do not critically question and discuss in the manuscript whether the symptoms are really due to the vaccination. In my view, this is unacceptable.

3. The authors do not provide any information on the medical history before the vaccinations. Were the patients all healthy before vaccination? Has there been a history of episodes with similar symptoms? E.g. Patient 2 (73y old) - were arterial hypertension and gonalgia really caused by vaccination or already known?

4. Unfortunately, information in the discussion is also incorrect and not well researched. E.g. the authors speak of "only a few case reports" about long-term side effects and cite reference 3 as an example, a patient diagnosed with Vaccine-induced immune thrombocytopenia - a specific immune-mediated side effect of the Covid vaccination. The pathogenesis of VITT

characterized within the last 1,5 years and has already been described in hundreds of patients in large studies from UK, Germany, and Scandinavia.

Reviewer #2:

Dear authors,

Thank you for your courage to submit such a novel paper!

Firstly, please correct your English language, sentences, typos, and do capitalize all words' initials before abbreviation parenthesis.

Secondly, please rewrite abstract's results more clearly, what do you mean about sarscov2 infection? Do you mean vaccination against covid19? please correct this phrase appropriately. Intro first line, correct your phrase, it is vaccination against covid-19 and not anti-sarscov2 vaccination.

BPV as an abbreviation is not correct, please remove the parenthesis.

Discussion: A recent review has discussed in the expert opinion paragraph all the reasons why side effects should be monitored for >4weeks. Please include this review article in your discussion appropriately, with that reference <https://doi.org/10.3390/diagnostics12071555>

Article: "Current Evidence in SARS-CoV-2 mRNA Vaccines and Post-Vaccination Adverse Reports: Knowns and Unknowns". Also, please discuss according to this reference, that up to now, there is no report for detecting spike protein and mRNA ingredients to the cerebrospinal fluid, and it should have been evident a study like that one.

Please write the conclusion paragraph with a title 'conclusion' so as to be clearly stated.

Good luck!

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Authors' response

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To: Prof. Heger

Editor in Chief

Journal of Clinical and Translational Research

Ref. Ms. No. JCTRes-D-22-00120

“Take long post-COVID vaccination syndrome seriously”

Dear Prof. Heger,,

Thank you for your email dating 12th September 2022, your and the reviewer's valuable comments, and for giving us the possibility to resubmit the manuscript. We revised the manuscript according to these suggestions with particular regards to the following points:

Reviewer #1:

The authors describe 5 patients with so-called long-post COVID vaccination syndrome following an anti-SARS-CoV-2 vaccination. All patients had a variety of symptoms that lasted longer than 6 months.

I share the authors' opinion that side effects after COVID19 vaccinations exist and patients with them should be taken seriously. For example, patients occasionally report long-lasting fatigue. I also agree that this is an important issue about which we do not yet have sufficient knowledge

Thank you.

Unfortunately, there are some difficulties in this manuscript. From my point of view, it can not be published in this form.

The authors introduce the paper by defining the LPCVS and explicitly point out that there are no or only mild findings in clinical or instrumental investigations for this syndrome. However, this definition does not apply to all patients described, since diagnostics to rule out organic causes have not (yet) been carried out or are not described in the manuscript. For example, the MRI is still pending for patient 1 and for patient 4 with facial paralysis no diagnostics are described at all (e.g. exclusion of other viral diseases, cranial imaging, etc.).

Investigations to clarify the complaints of patient 1 have been completed meanwhile and were non-informative. Their results were added to the result section. The extensive work-up in patient-4 is now described in detail.

I understand that it is of course difficult to prove that symptoms are due to a vaccination, since there is usually no specific diagnosis for causality. Nevertheless, diagnostics should at least be carried out to rule out other causes of the symptoms. Otherwise, it is not correct to attribute symptoms to a vaccination just because there is a temporal association (which does not yet prove a causality). In the case of the fourth patient in particular, I find it critical to attribute the symptoms to the vaccination, since a SARS-CoV-2 infection was detected at the same time and, as described above, no further diagnostics were carried out. The authors also do not critically question and discuss in the manuscript whether the symptoms are really due to the vaccination. In my view, this is unacceptable.

There was no simultaneous SARS-CoV-2 infection in patient 4. Results of the extensive diagnostic work-up in patient-4 were added to the case description. It is now argued that a causal relation between vaccination and LPCVS was suspected not only because of the temporal connection but also because the abnormalities were not present prior to vaccination.

The authors do not provide any information on the medical history before the vaccinations. Were the patients all healthy before vaccination? Has there been a history of episodes with similar symptoms? E.g. Patient 2 (73y old) - were arterial hypertension and gonalgia really caused by vaccination or already known?

The previous history was added to each patient. Similar complaints as after vaccination were not reported in any patient before vaccination. Arterial hypertension and gonalgia were definitively not present in pat. 2 before the vaccination. He did not take antihypertensive drugs before vaccination but had to take them since vaccination.

Unfortunately, information in the discussion is also incorrect and not well researched. E.g. the authors speak of "only a few case reports" about long-term side effects and cite reference 3 as an example, a patient diagnosed with Vaccine-induced immune thrombocytopenia - a specific immune-mediated side effect of the Covid vaccination. The pathogenesis of VITT characterized within the last 1,5 years and has already been described in hundreds of patients in large studies from UK, Germany, and Scandinavia.

We agree. The discussion was corrected accordingly. It is now stated that side effects are increasingly acknowledged and that VITT has meanwhile been described in several hundred patients.

Reviewer #2:

Thank you for your courage to submit such a novel paper!

Firstly, please correct your English language, sentences, typos, and do capitalize all words' initials before abbreviation parenthesis.

The English language grammatical errors and typos were corrected and words' initials are now capitalised before abbreviation

Secondly, please rewrite abstract's results more clearly, what do you mean about sarscov2 infection? Do you mean vaccination against covid19? please correct this phrase appropriately.

We mean anti-SARS-CoV-2 vaccination. The abstract was revised accordingly.

Intro first line, correct your phrase, it is vaccination against covid-19 and not anti-sarscov2 vaccination.

The sentence was corrected accordingly.

BPV as an abbreviation is not correct, please remove the parenthesis.

The abbreviation was omitted.

Discussion: A recent review has discussed in the expert opinion paragraph all the reasons why side effects should be monitored for >4weeks. Please include this review article in your discussion appropriately, with that reference

<https://doi.org/10.3390/diagnostics12071555> Article: "Current Evidence in SARS-CoV-2 mRNA Vaccines and Post-Vaccination Adverse Reports: Knowns and Unknowns". Also, please discuss according to this reference, that up to now, there is no report for detecting spike protein and mRNA ingredients to the cerebrospinal fluid, and it should have been evident a study like that one.

Thank you for drawing my attention to this great article. The paper is now discussed and we added that neither the spike protein nor mRNA ingredients have been detected in the CSF so far. The article was added to the list of references.

Please write the conclusion paragraph with a title 'conclusion' so as to be clearly stated. Good luck!

Was changed accordingly.

May we re-submit the manuscript entitled “Take long-postCOVID vaccination syndrome seriously?” by Finsterer J and Scorza F for publication as an original study in the journal “Journal of Clinical and Translational Research”.

The manuscript has not been published, submitted or is not simultaneously being submitted elsewhere, and no portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes. There is no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interest of the authors, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work. All authors contributed significantly, are in agreement with the content, and approved submission of the manuscript.

Please confirm receipt of the manuscript.

Sincerely Yours,

J. Finsterer, MD, PhD

Vienna, 13th September 2022

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2<sup>nd</sup> Editorial decision  
20-Oct-2022

Ref.: Ms. No. JCTRes-D-22-00120R1  
Take long post-COVID vaccination syndrome seriously  
Journal of Clinical and Translational Research

Dear Dr. Finsterer,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be

pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Nov 19, 2022.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Dear authors,

We have received reviewer comments in a second round pertaining to the aboverferenced manuscript, which I have pasted below.

Reviewer 1 is a very critical Hercule Poirot and found that 1 patient you seem to be describing was not properly referenced in your article as having been addressed in another paper. This has automatically raised flags within the editorial board, especially since this was a recurrent comment.

Could you please explain to us what is going on? We do not want to risk the carefully built reputation of the journal, even if it is merely optics that are not rooted in any truth.

There are also other issues that will have to be dealt with.

If you manage to provide a sufficient response, I will proceed with handling the manuscript.

Otherwise I fear that I will have to reject the paper.

Thank you and kindest regards,

Michal Heger  
Editor

Reviewers' comments:

Reviewer #1: The authors submitted a revised version of their manuscript and supplemented the patients' history, as well as expanded the discussion, what I appreciate. In the following, I would like to set out a few points which, in my point of view, are unfortunately not acceptable for publication.

1. The authors already described one patient with LPCVS (=Reference 2) in another publication. This publication has now been published and is available online. The 45-year old patient described in reference 2 seems to be the same patient as described in this manuscript as patient 4. The characteristics, medical history, symptoms, and investigations were the same. The authors did not mention that this patient has already been described elsewhere,

although reference 2 has been given in the introduction.

However, the authors state, that "clinical manifestations in the five patients were attributed to the vaccination because they were absent prior to vaccination." In reference 2 it is written that the patient (assuming it is the same patient as patient 4 in this manuscript) has a history of vertigo since she was 21 years old (the symptom she also had after COVID-vaccination) This information is not given in this manuscript. It is not clear to me why exactly this information has been omitted here.

2. Previously, it was noted that the given references in the discussion did not correspond to the statements made by the authors. The authors have expanded their discussion part on VITT, what I really appreciate. Nevertheless, the authors have added reference 3 as a reference for VITT. This is a review of patients with TTP after vaccination (not VITT! - two different diseases). The reference is not appropriate.

3. There are some inconsistencies in the text even after revision. For example, the first section of the results describes that patients' symptoms appeared after 2nd or 3rd vaccination. In the detailed description of patient 1, however, first scotoma are then described after 1st vaccination.

4. In my opinion, the diagnostics carried out to exclude other causes are still not sufficient to classify the symptoms exclusively as a vaccine side effect, especially in patient 5. The patient with facial paresis has not been examined by a neurologist, imaging or diagnostics for other causes (e.g. other viral diseases) has not been described. In my view, the temporal association is not sufficient enough.

I agree with the authors that the topic of "long-term side effects after vaccinations" is important and needs more attention. Since the authors have found several patients in a very short time that they believe meet the definition of LPCVS, I would recommend that the authors extend their observation period to collect even more patients. Perhaps "typical patterns" can be defined.

Reviewer #2: A very well revision  
It is accepted by me,  
looking forward to your publication!

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Authors' response

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To: Prof. Heger  
Editor in Chief



Ref. Ms. No. JCTRes-D-22-00120R1

“Take long post-COVID vaccination syndrome seriously”

Dear Prof. Heger,

Thank you for your email dating 12th September 2022, your and the reviewer’s valuable comments, and for giving us the possibility to resubmit the manuscript. We revised the manuscript according to these suggestions with particular regards to the following points:

Reviewer #1:

The authors submitted a revised version of their manuscript and supplemented the patients' history, as well as expanded the discussion, what I appreciate. In the following, I would like to set out a few points which, in my point of view, are unfortunately not acceptable for publication.

1. The authors already described one patient with LPCVS (=Reference 2) in another publication. This publication has now been published and is available online. The 45-year old patient described in reference 2 seems to be the same patient as described in this manuscript as patient 4. The characteristics, medical history, symptoms, and investigations were the same. The authors did not mention that this patient has already been described elsewhere, although reference 2 has been given in the introduction. However, the authors state, that "clinical manifestations in the five patients were attributed to the vaccination because they were absent prior to vaccination." In reference 2 it is written that the patient (assuming it is the same patient as patient 4 in this manuscript) has a history of vertigo since she was 21 years old (the symptom she also had after COVID-vaccination) This information is not given in this manuscript. It is not clear to me why exactly this information has been omitted here.

To avoid any repetition, patient 4 was omitted from the evaluation

2. Previously, it was noted that the given references in the discussion did not correspond to the statements made by the authors. The authors have expanded their discussion part on VITT, what I really appreciate. Nevertheless, the authors have added reference 3 as a reference for VITT. This is a review of patients with TTP after vaccination (not VITT! - two different diseases). The reference is not appropriate.

Thank you for your vigilance. Current reference 3 was replaced by an appropriate article.

3. There are some inconsistencies in the text even after revision. For example, the first section of the results describes that patients' symptoms appeared after 2nd or 3rd vaccination. In the detailed description of patient 1, however, first scotoma are then described after 1st vaccination.

Scotoma in patient-1 after the first doses lasted for only a few minutes. Thus, it was not persisting and therefore not LPCVS. The scintillating scotoma that developed after the second dose persisted, which is why LPCVS started after the second dose not after the first..

4. In my opinion, the diagnostics carried out to exclude other causes are still not sufficient to classify the symptoms exclusively as a vaccine side effect, especially in patient 5. The patient with facial paresis has not been examined by a neurologist, imaging or diagnostics for other causes (e.g. other viral diseases) has not been described. In my view, the temporal association is not sufficient enough.

We omitted patient-5 from the evaluation

I agree with the authors that the topic of "long-term side effects after vaccinations" is important and needs more attention. Since the authors have found several patients in a very short time that they believe meet the definition of LPCVS, I would recommend that the authors extend their observation period to collect even more patients. Perhaps "typical patterns" can be defined.

The accumulation occurred because we systematically looked for these patients during the observational period. Afterwards, we no longer searched systematically for LPCVS patients.

May we re-submit the manuscript entitled “Take long-post COVID vaccination syndrome seriously?” by Finsterer J and Scorza F for publication as an original study in the journal “Journal of Clinical and Translational Research”.

The manuscript has not been published, submitted or is not simultaneously being submitted elsewhere, and no portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes. There is no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interest of the authors, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work. All authors contributed significantly, are in agreement with the content, and approved submission of the manuscript.

Please confirm receipt of the manuscript.

Sincerely Yours,

J. Finsterer, MD, PhD

Vienna, 15<sup>th</sup> October 2022

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3<sup>rd</sup> Editorial decision  
20-Oct-2022

Ref.: Ms. No. JCTRes-D-22-00120R2  
Take long post-COVID vaccination syndrome seriously  
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at <http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Nov 19, 2022.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for addressing the reviewer's comments in the second review round.

I have gone through the paper and we are willing to accept the paper as a case series pending the following non-negotiable modifications.

1) The strength of the language, and mainly conclusions, must be tones down because your case presentation is solely based on 3 patients, which hardly qualifies as a robust cohort size. Examples of language softening include, but are not limited to:

- Title should read: Clinically confirmed long post-COVID vaccination syndrome should be taken seriously
- Conclusion abstract: SARS-CoV-2 vaccinations may cause not only short-term but also long-term side effects (may cause instead of cause)
- It is well known that vaccinations against COVID-19 are not free from side effects in some

patients [1]. (inserted some patients)  
etc.

Please continue modifying the rest of the manuscript along these lines.

We are looking forward to your resubmission.

Michal Heger  
Editor

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Authors' response

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To: Prof. Heger  
Editor in Chief  
Journal of Clinical and Translational Research

Ref. Ms. No. JCTRes-D-22-00120R2  
“Clinically confirmed long post-COVID vaccination syndrome should be taken seriously”

Dear Prof. Heger,

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Examples of language softening include, but are not limited to:

Strength of language and conclusions were toned down

We hereby re-submit the manuscript entitled “Clinically confirmed long-post COVID vaccination syndrome should be taken seriously?” by Finsterer J and Scorza F for publication as an original study in the journal “Journal of Clinical and Translational Research”.

The manuscript has not been published, submitted or is not simultaneously being submitted elsewhere, and no portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes. There is no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interest of the authors, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work. All authors contributed significantly, are in agreement with the content, and approved submission of the manuscript.

Please confirm receipt of the manuscript.

Sincerely Yours,

J. Finsterer, MD, PhD

Vienna, 22<sup>nd</sup> October 2022

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4<sup>th</sup> Editorial decision  
24-Oct-2022

Ref.: Ms. No. JCTRes-D-22-00120R3  
Clinically confirmed long post-COVID vaccination syndrome should be taken seriously  
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Comments from the editors and reviewers: