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Addressing the global surge of COVID-19 cases: insights from diagnostics, improved treatment strategies, vaccine development and application

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Addressing the Global Surge of COVID-19 Cases: Insights from Diagnostics, Improved Treatment Strategies, Vaccine Development and Application
Journal of Clinical and Translational Research

Dear Dr Olayemi,

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 and attached to this email. In addition to the reviewers' comments, please provide more depth to the manuscript. For example, the pros and cons of each addressed treatment could be indicated. For example,

Remdesivir needs to be stored at very low temperatures, which limits its distribution infrastructure. Also, the antiviral is administered intravenously to select patients and the clinical benefits are not that profound (see the statistics on reduction in hospital stay and mortality). It is important to be realistic about the proposed therapeutics.

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 Dec 19, 2020.

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: Article is timely and has helpful information, however the review is too broad and touches bare minimum of everything. Although information is useful to all font line workers, it needs extensive revision including English grammar and redundancy. For example New and novel is redundant. Do not use magic bullets (on page 3, line 28-29), there is confusion in using SARS-CoV-2 (virus) and COVID-19 (Diseases).

Page 6, line 18: "Meanwhile, several diagnostic tests are available for COVID-19 patients, up till date there is no reference-standard test otherwise known as "gold standard" for SARS-CoV-2 tests." RT-PCR is considered gold standard, cherry picked RT-PCR false negativity rates.

Reviewer #2: Dear Author,
In my opinion, the following changes should be provided in text:
1 - Page 3, line 31 - Add more drugs repurposed and references. More than 30 clinical trials with repuposed drugs have been done up to now. This information is very important to be in the text.
2 - Page 3, line 33 - Make a precise relationship between the adverse effects and each drug, citing the drug.
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4 - Page 5, lines 17 and 29 - Change COVID-19 for the virus name, SARS-CoV-2.
5 - Page 8, lines 1-19 - The author should cite examples of these drugs repurposed and its possible sinergistic mechanism. Written like this, looks like it is beeing sugested a combination of the two antivirals: Lop-Rit and Remdesivir. Such combination may induce

serious adverse effects.
6 - Page 8 - Author should cite the original diseases of these treatments: Lop-Rit - AIDS; Remdesivir - Ebola virus infection.
Also, the ACTT study has already been finished and published with data shown that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Remdesivir is also approved by FDA for emergencial use. All these data should be actualized in this section. (https://www.fda.gov/drugs/drug-safety-and-availability/fdas-approval-veklury-remdesivir-treatment-covid-19-science-safety-and-effectiveness)
7 - Page 10, line 8 - The author should explain what "Ig" is, in its first appearence on the text, and include this in the abbreviation section.
8 - Page 8, 1° paragraph - It is very important to cite in the text that one product by AbCelleraBio/Lilly (Bamlanivimab) has an emergency use approved by FDA. https://www.fda.gov/media/143602/download. Also, phases II/III clinical trials are undergoing with 2 antibody products: Celltrion (CT-P59/Placebo) and Regeneron (RECOVERY trial):
https://clinicaltrials.gov/ct2/show/NCT04602000
https://www.celltrionhealthcare.com/en-us/board/noticedetail?modify_key=176&pagenumber=1&keyword=covid&keyword_type=
https://investor.regeneron.com/news-releases/news-release-details/recovery-trial-data-monitoring-committee-recommends-continuing
https://clinicaltrials.gov/ct2/show/NCT04452318

Reviewer #3: Reviewer's comment
Major comments:
Page 5, Line 13-16: The authors referenced "Adedokun, KA. Emerging Neuropathological and Acid-Base Disorders in COVID-19: A Possible Diagnostic Utility in Containment Operations. Open Access Maced J Med Sci" to expressed concern about failure of current testing methods to detect asymptomatic carriers of COVID-19. However, the authors did not include what type(s) of tests were used in the referenced article. Is it a serologic, antigen, or a PCR based test?

Page 8, Line 22-24:
i. The authors claim that "RVTPs will circumvent the sampling and transportation errors which have contributed to the bane of testing" without previously identifying any specific sampling or transportation error(s) in current COVID-19 testing methods. This claim need explanation or a reference to support this claim.
ii. Author also need to explain how RVTPs compared to current methods can rapidly detect COVID-19 infection. Is this in terms of TAT or early detection of infection by COVID-19?
iii. What does "a good reference point" means as used by the authors in line 24?

Minor comment:
Page 11, Line 12-13: Change "Hybridoma technology could circumvent the need to pool

intravenously or recruit from patients who recovered from…." to "Hybridoma technology could circumvent the need to pool intravenously or recruit patients who recovered from…".

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' response

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December 7, 2020

Re: revision Ms. No. JCTRes-D-20-00121

Dear Dr. Michal Heger,

Thank you for giving us an opportunity to resubmit a revised version of our manuscript entitled "Addressing the Global Surge of COVID-19 Cases: Insights from Diagnostics, Improved Treatment Strategies, Vaccine Development and Application."

We have addressed all comments of the reviewers using the track changes function in Word (attached as supplementary material not for publication). Moreover, every modification or rebuttal of the reviewer's comments is detailed per comment below in red italics.

We are grateful for the useful comments of the reviewers, as a result of which the paper has been considerably improved.

REVIEWER COMMENTS

Reviewer #1:

Article is timely and has helpful information, however the review is too broad and touches bare minimum of everything. Although information is useful to all front line workers, it needs extensive revision including Engli sh grammar and redundancy. For example New and novel is redundant.

We are grateful for your commentary and suggestions, which we have addressed to the fullest extent as indicated below for every one of your comments.

L7 pg3, L6 pg4, (all "novel" that exists in redundancy along with "new" were deleted/corrected)

Do not use magic bullets (on page 3, line 28-29), there is confusion in using SARS-CoV-2 (virus) and COVID-19 (Diseases).

A. We want to appreciate your suggestions as a constructive redirection to a better article.

On the use of "magic bullet", we respect the opinion of the reviewer very much who has contributed immensely in this project; we equally want to add that "magic bullet" is not a jargon but now a pharmacological term. It is a scientific concept developed by a German Nobel laureate Paul Ehrlich in 1900 (1-4). Ehrlich's discovery of Salvarsan in 1909 for the treatment of syphilis is termed as the first magic bullet. This led to the foundation of the concept of chemotherapy (5-8).

In the field of medicine and pharmacology today, magic bullet means a drug candidate in trial - the perfect choice in this sentence wherein several therapeutic agents were put into trial in the context of COVID-19, read as "*several therapeutic agents have been tested against SARS-CoV-2, so far, very few magic bullets remain hopeful*". We therefore, used this word to unveil the background information of ongoing investigative therapeutic trial from possible drug agents with perfect hit (magic bullet). The connotation we believe would give more information as regards the subject of our discussion. Sir/Ma, you may want to confirm our **references (both medical dictionaries and the associated articles) below;**

MEDICAL DICTIONARY:

magic bullet. (n.d.) The American Heritage® Medical Dictionary. (2007). Retrieved November 28 2020 from https://medical-dictionary.thefreedictionary.com/magic+bullet

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ARTICLES:

[1.] Tan, SY; Grimes, S (2010). "Paul Ehrlich (1854-1915): man with the magic bullet" (PDF). Singapore Medical Journal. 51 (11): 842–843. PMID 21140107.
[2.] Strebhardt, Klaus; Ullrich, Axel (2008). "Paul Ehrlich's magic bullet concept: 100 years of progress". Nature Reviews Cancer. 8 (6): 473–480. doi:10.1038/nrc2394. PMID 18469827. S2CID 30063909.
[3.] Heynick, F. (2009). "The original 'magic bullet' is 100 years old - extra". The British Journal of Psychiatry. 195 (5): 456. doi:10.1192/bjp.195.5.456. PMID 19880937.
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[6.] Chuaire, Lilian; Cediel, Juan Fernando (2009). "Paul Ehrlich: From magic bullets to chemotherapy". Colombia Médica. 39 (3): online.
[7.] Nigel, Kelly; Rees, Bob; Shuter, Paul (2002). Medicine Through Time (2nd ed.). Oxford (UK): Heinemann Educational Publishers. pp. 90–92. ISBN 978-0-435-30841-4.

[8.] Lederer, S. E.; Parascandola, J. (998). "Screening Syphilis: Dr. Ehrlich's Magic Bullet Meets the Public Health Service". Journal of the History of Medicine and Allied Sciences. 53 (4): 345–370. doi:10.1093/jhmas/53.4.345. PMID 9816818.

B. L7 pg 6,

Page 6, line 18: "Meanwhile, several diagnostic tests are available for COVID-19 patients, up till date there is no reference-standard test otherwise known as "gold standard" for SARS-CoV-2 tests." RT-PCR is considered gold standard, cherry picked RT-PCR false negativity rates.

- We have edited and revised this part of the text to avoid any misinformation by using your suggestion accordingly.

Reviewer #2:

In my opinion, the following changes should be provided in text:
1 - Page 3, line 31 - Add more drugs repurposed and references. More than 30 clinical trials with repurposed drugs have been done up to now. This information is very important to be in the text.

2 - Page 3, line 33 - Make a precise relationship between the adverse effects and each drug, citing the drug.

- More repurposed drugs have been included in the manuscript with additional reference as stated below

Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;323(18):1824-1836. doi: 10.1001/jama.2020.6019. PMID: 32282022.

Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19(3):149-150. doi: 10.1038/d41573-020-00016-0. PMID: 32127666.

https://link.springer.com/article/10.1007/s42399-020-00485-9/tables/1

https://link.springer.com/article/10.1007/s42399-020-00485-9

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10. Uzun T, Toptas O. Artesunate: could be an alternative drug to chloroquine in COVID-19 treatment? Chin Med. 2020;15:54. doi: 10.1186/s13020-020-00336-8.

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12. ClinicalTrials.gov; US National Library of Medicine. Evaluating the Efficacy of Artesunate in Adults With Mild Symptoms of COVID-19. 2020. Identifier: NCT04387240, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04387240 Accessed 02 December 2020.

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15. Tripathy S, Dassarma B, Roy S, Chabalala H, Matsabisa MG. A review on possible modes of action of chloroquine/hydroxychloroquine: repurposing against SAR-CoV-2 (COVID-19) pandemic. Int J Antimicrob Agents. 2020;56(2):106028. doi: 10.1016/j.ijantimicag.2020.106028.

16. ClinicalTrials.gov; US National Library of Medicine. Chloroquine Phosphate Prophylactic Use in Health Personnel Exposed to COVID-19 Patients. Identifier: NCT04443270, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04443270 . Accessed 02 December 2020.

17. ClinicalTrials.gov; US National Library of Medicine. Norwegian Coronavirus Disease 2019 Study (NO COVID-19). Identifier: NCT04316377, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04316377. Accessed 03 December 2020.

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19. ClinicalTrials.gov; US National Library of Medicine. A Multicentre Open-label Two-arm Randomised Superiority Clinical Trial of Azithromycin Versus Usual Care In Ambulatory COVID19 (ATOMIC2) (ATOMIC2). Identifier: NCT04381962, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04381962. Accessed 03 December 2020.

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21. Li H, Liu DH, Chen LL, Zhao Q, Yu YZ, Ding JJ, Miao LY, Xiao YL, Cai HR, Zhang DP, Guo YB, Xie CM. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. Antimicrob Agents Chemother. 2014;58(1):511-7. doi: 10.1128/AAC.02067-13.

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23. Avastin (Bevacizumab) side effects drug center: RX List. 2020. Retrieved 4 December, 2020. Available from: https://www.rxlist.com/avastin-side-effects-drug-center.htm

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27. ClinicalTrials.gov; US National Library of Medicine. Antioxidant Therapy for COVID-19 Study (GSHSOD-COVID). Identifier: NCT04466657, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04466657. Accessed 03 December 2020.

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29. Vitamins, herbs, dietary supplements: N-acetyl cysteine: RX List. 2020. Retrieved 4 December, 2020. Available from: https://www.rxlist.com/n-acetyl_cysteine/supplements.htm#SafetyConcerns

Table 1: Selected repurposed therapeutic agents in COVID-19 clinical trials and possible adverse effects

Therapeutic class	Repurposed agents/intervention	Stage/expected completion date	Mode of action	Possible adverse effects	Trial registration	Locations	References
Anti-virals	Remdesivir	Phase III/II / March 2022	Inhibits viral RNA-dependent polymerase and induces a negative proofreading activity (**See fig. 2**).	Respiratory failure and organ impairment, anaphylactoid reactions, heart rhythm disorders angioedema, diarrhea, skin rash, and hypotension, among others.	NCT04575064	Germany	[6, 7]
	Lopinavir/ Ritonavir	Phase III/ March, 2021	Lopinavir is a peptidomimetic protease inhibitor combined with ritonavir. (**See fig. 2**). Targets the main protease (Mpro) of SARS-CoV-2, a key protease enzyme required for the virus to replicate and assemble itself.	Allergic reaction, erectile dysfunction, libido, arrhythmia, abdominal pain, hyperlipidemia, nausea, among many others.	NCT04364022	Switzerland	[7, 8]
	Favipiravir	Phase III/September, 2020	Inhibits the viral RNA synthesis through RNA-dependent RNA	Impaired erythropoiesis. High concerns for gestational		China	[7, 9]

			polymerase (RdRP, RDR) inhibition.	problems such as embryonic premature death and teratogenicity or congenital consequences.	NCT04425460		
Anti-malarials	Artemisinin / Artesunate	Phase II/ April, 2021	Possesses anti-inflammatory properties, such as inhibition of IL-6 that plays a key role in the development of severe COVID-19 and cytokine storm. Also inhibits NF-kB and viral protein synthesis, thus disrupting the viral replication process at early phase.	Possible parasite mutation may bolster drug-resistant strains (especially, in areas with endemicity of Plasmodium falciparum). Also, possibility of haemolytic anemia, severe allergic reactions and kidney failure.	NCT04387240	Saudi Arabia	[10 - 13]
	Chloroquine phosphate	Phase 1/ January, 2021	Inhibits glycosylation of the cellular ACE-2 receptor thereby interferes with binding of virus to the cell receptor. Also Increases endosomal pH, thus interfering with fusion of SARS-CoV-2 and the host cell membranes	Cardiac problems. Retinopathy. Possibility of bone marrow suppression. Hypoglycemia, rash, and nausea.	NCT04443270	Mexico	[14 - 16]
	Hydroxychloroquine tablet	Phase IV/ March, 2025	Increases endosomal pH, and interferes with SARS-CoV-2 binding. Inhibition of cytokine storm.	Ditto	NCT04316377	Europe	[15, 17]
Antibiotics	Azithromycin	Phase III/ September, 2020	Possesses antiviral properties by preventing virus entry into cells, and replication. Enhances immune	Risk of bacterial resistance, hearing impairments, and pulmonary problems, on long term use.	NCT04381962	United Kingdom	[18 - 21]

			response against the virus, by upregulating the syntheses of type I and III interferons - particularly interferon-β and interferon-λ. Antibacterial properties by inhibiting bacterial protein synthesis, thus preventing secondary infection.				
Anti-tumour	Bevacizumab	Phase II/ Completed	Binds circulating VEGF and blocks its receptor binding, effectively inhibiting downstream signaling and preventing angiogenesis, lymphangiogenesis, and potential edematous effect. VEGF is upregulated in COVID-19, and thus may contribute to pulmonary edema, leading to ARDS and ALI.	Possibilities of increased risk of infection, high blood pressure, peripheral neuropathy, nosebleed, rectal bleeding, headache, back pain, dry/watery eyes, dry/flaky skin, runny nose, sneezing, and changes in sense of taste.	NCT04275414	China	[22, 23]
Others							
Monoclonal antibody(Interleukin-6 inhibitor)	Sarilumab	Phase II/III /Completed	A human monoclonal antibody binds to IL-6 receptors that inhibit IL-6-mediated signaling (IL-6 antagonist). In COVID-19, the IL-6 cytokine is	There are possibilities for anaphylactoid reactions, rash, urticaria, gastrointestinal perforation and new primary malignancy. There is high accidental	NCT04315298	United States	[24, 25]

			plays a vital role in the inflammatory process and response in body system.	drug-drug interactions with several medications and vaccines. Serious concern for possible deadly infections. Active TB, invasive fungal, bacterial, viral, and other opportunistic infections have been experienced in patients receiving sarilumab.			
Natural products	Omega-3, Nigella Sativa, Indian Costus, Quinine, Anise Seed, Deglycyrrhizinated Licorice, Artemisinin, Febrifugine	Phase II/III /December, 04 2020	Clinical immunity boosting to effective antiviral effect. Omeg-3 as an example affect the human health by many mechanisms e.g. Anti-oxidant, immunity boosting agent. Moreover, Omega-3 exerts an antiviral effect on Flu virus by inhibiting influenza virus replication 1. On the other hand, black seed supplementation exerts a chelation effect on sickle cell anemia patients and inhibits Human Heme Metabolism 2. Moreover, black seed exerts an antiviral effect on the replication of old coronavirus and the expression of (TRP-genes)	-	NCT04553705	Saudi Arabia	[26]

			family 3. In addition, Omega-3 regulates the human immunity against bacterial and viral infections				
Dietary Supplement	Antioxidant formulation(reduced GSH, NAC, SOD and bovine lactoferrin and immunoglobulin)	Not Applicable/ April, 2021	Reactive oxygen species induce oxidative stress responses and thereby provoke acute lung injury (clinical feature of COVID-19 disease). Thus, antioxidant measure is expected to ameliorate or prevent the effect of oxidative damage. NAC can change the redox balance towards reduced status inside neutrophils by GSH, which suppresses NF-κB activation at concentrations of 10mM or more, resulting in modulation of cytokine production and chemotactic signals	Gastrointestinal disturbances and diarrhea are possible. Also, NAC is known to cause bleeding disorder and has high probability of drug interactions with some medications.	NCT04466657	Nigeria	[27 - 29]

KEY- ACE-2: Angiotensin-converting enzyme 2; ARD: Acute respiratory distress syndrome; ALI: Acute lung injury; GSH: Reduced glutathione; IL-6: Interleulin-6; NAC: N-acetylcysteine; NF-kB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; SOD: Superoxide dismutase; VEGF: vascular endothelial-derived growth factor

1. Drug Trials Snapshots: Artesunate". U.S. Food and Drug Administration (FDA). 2020. Retrieved 29 November, 2020
2. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Hydroxychloroquine. [Updated 2018 Mar 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548738/

3 - Page 4, line 10 - It is very important to point that these vaccines are not approved yet for these diseases (MERS and SARS).

- This part have been revised appropriately

4 - Page 5, lines 17 and 29 - Change COVID-19 for the virus name, SARS-CoV-2.

- This part have been revised appropriately

5 - Page 8, lines 1-19 - The author should cite examples of these drugs repurposed and its possible sinergistic mechanism. Written like this, looks like it is being suggested a combination of the two antivirals: Lop-Rit and Remdesivir. Such combination may induce serious adverse effects.

- An explanation of the possible synergistic mechanisms with examples of the antiviral drugs highlighted in this part of the text has been given and revised.

6 - Page 8 - Author should cite the original diseases of these treatments: Lop-Rit - AIDS; Remdesivir - Ebola virus infection.Also, the ACTT study has already been finished and published with data shown that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Remdesivir is also approved by FDA for emergencial use. All these data should be actualized in this section. (https://www.fda.gov/drugs/drug-safety-and-availability/fdas-approval-veklury-remdesivir-treatment-covid-19-science-safety-and-effectiveness)

7 - Page 10, line 8 - The author should explain what "Ig" is, in its first appearence on the text, and include this in the abbreviation section.

8 - Page 8, 1° paragraph - It is very important to cite in the text that one product by AbCelleraBio/Lilly (Bamlanivimab) has an emergency use approved by FDA.

https://www.fda.gov/media/143602/download. Also, phases II/III clinical trials are undergoing with 2 antibody products: Celltrion (CT-P59/Placebo) and Regeneron (RECOVERY trial):

https://clinicaltrials.gov/ct2/show/NCT04602000

https://www.celltrionhealthcare.com/en-us/board/noticedetail?modify_key=176&pagenumber=1&keyword=covid&keyword_type=

https://investor.regeneron.com/news-releases/news-release-details/recovery-trial-data-monitoring- committee-recommends-continuing

https://clinicaltrials.gov/ct2/show/NCT04452318

- These parts have been revised appropriately. We have captured current data on the efficacy of Remdesivir, which was recently granted an emergency use authorization approval by the FDA for use in peadiatric and adult patients with COVID-19. Recent data on other trial drugs like Bamlanivimab are also captured and included in this part of the text. Thus, this entire part of the text has been carefully revised.

Reviewer #3:

Reviewer's comment

Major comments:

Page 5, Line 13-16: The authors referenced "Adedokun, KA. Emerging Neuropathological and Acid-Base Disorders in COVID-19: A Possible Diagnostic Utility in Containment Operations. Open Access Maced J Med Sci" to expressed concern about failure of current testing methods to detect asymptomatic carriers of COVID-19. However, the authors did not include what type(s) of tests were used in the referenced article. Is it a serologic, antigen, or a PCR based test?

- This part has been revised appropriately to include antibody based test.

Page 8, Line 22-24:

i. The authors claim that "RVTPs will circumvent the sampling and transportation errors which have contributed to the bane of testing" without previously identifying any specific sampling or transportation error(s) in current COVID-19 testing methods. This claim need explanation or a reference to support this claim.

   - This part has been revised appropriately with additional explanation to substantiate the reasons for the claim made.

ii. Author also need to explain how RVTPs compared to current methods can rapidly detect COVID-19 infection. Is this in terms of TAT or early detection of infection by COVID-19?

   - This part have been revised appropriately

iii. What does "a good reference point" means as used by the authors in line 24?

- This part has been revised as appropriately to include good reference option in place of the used term.

Minor comment:

Page 11, Line 12-13: Change “Hybridoma technology could circumvent the need to pool intravenously or recruit **from** patients who recovered from….” to “Hybridoma technology could circumvent the need to pool intravenously or recruit patients who recovered from…”.

- These parts of the text have been edited accordingly.

2nd Editorial decision
25-Dec-2020

Ref.: Ms. No. JCTRes-D-20-00121R1
Addressing the Global Surge of COVID-19 Cases: Insights from Diagnostics, Improved Treatment Strategies, Vaccine Development and Application
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 Jan 24, 2021.

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 #2: Dear author,

Some specific corrections should be done in the text and table 1.
1 - On page 2, nitazoxanide and nafamostat are not anti-virals. Correct this, writing the correct classification.
2 - In table 1, the word "ditto" is not clear enough. You should write the specific adverse effects of hydroxychloroquine.

Reviewer #3: Dear Authors,

Thanks for the prompt and detailed response to the reviewers' comment. The efforts you put into this manuscript is a commendable one. This is a topic that needs constant revision based on the nature of SARS-CoV-2 and the devastation it has caused humanity.

I wish you more successes.

Authors' response

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December 28, 2020

Re: revision Ms. No. JCTRes-D-20-00121

Dear Dr. Michal Heger,

Thank you for giving us an opportunity to resubmit a revised version of our manuscript entitled "Addressing the Global Surge of COVID-19 Cases: Insights from Diagnostics, Improved Treatment Strategies, Vaccine Development and Application."

We have addressed all comments of the reviewers using the track changes function in Word (attached as supplementary material not for publication). Moreover, every modification or rebuttal of the reviewer's comments is detailed per comment below in red italics.

We are grateful for the useful comments of the reviewers, as a result of which the paper has been considerably improved.

On behalf of the authors, kindest regards,

Lawal O. Olayemi

—

REVIEWER COMMENTS

Reviewer #2:

Some specific corrections should be done in the text and table 1.
1 - On page 2, nitazoxanide and nafamostat are not anti-virals. Correct this, writing the correct classification.
2 - In table 1, the word "ditto" is not clear enough. You should write the specific adverse effects of hydroxychloroquine.

Thank you for your comments. We have addressed these minor errors in the text as indicated below.

- 1. Though we appreciate the reviewer's observation, but in previous studies and documented literature nitazonamide has shown to be a broad spectrum antiviral agent. However, the two drugs; Nitazoxanide and Nafamostat have been re-classified in the text to include: Nitazonamide (broad spectrum anti-parasitic) and Nafamostat (broad spectrum synthetic serine protease inhibitor).

-2. The word "ditto" has been edited and the specific adverse effects of Hydroxychloroquine has been included to comprise; headaches, retinopathy, dizziness, gastrointestinal upset, myopathy, hypoglycemia, irregular heartbeat, rash, and nausea.

Reviewer #3: Dear Authors,

Thanks for the prompt and detailed response to the reviewers' comment. The efforts you put into this manuscript is a commendable one. This is a topic that needs constant revision based on the nature of SARS-CoV-2 and the devastation it has caused humanity.

- *We really appreciate your constructive criticism in making the manuscript more suitable and adaptable. Your encouragement and feedback is highly welcome.*

3rd Editorial decision
29-Dec-2020

Ref.: Ms. No. JCTRes-D-20-00121R2
Addressing the Global Surge of COVID-19 Cases: Insights from Diagnostics, Improved Treatment Strategies, Vaccine Development and Application
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 Jan 28, 2021.

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 submitting a revised version of your manuscript.

Two items remain before we can proceed to publication:

1) please proofread the text and eliminate residual spelling and grammar errors.
2) three vaccines have now been approved (Pfizer/BioNTech, AZ, Moderna). Please update the text at your earliest convenience to reflect the latest developments in the vaccine niche.

Thank you,

Michal Heger
Editor

Authors' response

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January 5, 2020

Re: revision Ms. No. JCTRes-D-20-00121

Dear Dr. Michal Heger,

Thank you for giving us an opportunity to resubmit a revised version of our manuscript entitled "Addressing the Global Surge of COVID-19 Cases: Insights from Diagnostics, Improved Treatment Strategies, Vaccine Development and Application."

We have addressed all comments of the reviewers using the track changes function in Word. Moreover, every modification of the reviewer's comments is detailed per comment below in red italics. Please note also that COVID-19 is fast re-evolving and our paper was based on the situation at the time. We believed that this study will provide direction for future researches in addressing other potential questions surrounding the pandemic, especially on vaccine developments. We trust in your expedited decision without further delay of the manuscript for a positive outcome.

We are grateful for the useful comments of the reviewers, as a result of which the paper has been considerably improved.

On behalf of the authors, kindest regards,

Lawal O. Olayemi

REVIEWER COMMENTS

Thank you for submitting a revised version of your manuscript.

Two items remain before we can proceed to publication:

1) Please proofread the text and eliminate residual spelling and grammar errors.

- Thank you for your comments. We have addressed these minor errors in the text

2) three vaccines have now been approved (Pfizer/BioNTech, AZ, Moderna). Please update the text at your earliest convenience to reflect the latest developments in the vaccine niche.

- Though we appreciate the reviewer's observation, but as mentioned earlier, discussion surrounding COVID-19 vaccine developments and their efficacy is still a subject of unending debate.

We have revised the part on vaccine niche to include the following;

- 3.4.2 Authorization of emergency COVID-19 vaccines with many unanswered questions

There is good news about the emergency use authorizations (EUAs) of COVID-19 vaccines sponsored by the Pfizer/BioNTech, Moderna and AztraZeneca. The U.S.- FDA has recently approved some new recombinant protein-based, non-replicating subunit RNA vaccines against COVID-19. So far, the Phase 3 clinical trial results show that these vaccines can be safe and effective for use. However, this is EUA and not a full approval. According to the FDA [76],

EUA is given when adequate and approved alternatives are unavailable; it does not mean these vaccines are completely risk-free.

It is believed that the current demanding COVID-19 situations in places like the United States and some parts of the Europe had called for the emergency authorization. Many questions in association with these vaccines are yet unanswered. It is reasonable to accept that there are potential risks and fears of unknown regarding these new vaccines. But making these vaccines hastily available than the usual process should be less contemplated against the risk of infection with COVID-19 itself. However, it is believed that when productions of these vaccines increase and become more readily available and when many populations are vaccinated, there could be possible emergence of unknowns at any time. These unknowns will prompt scientists to continue to ask questions. It is important that some of the puzzles about emergency use of COVID-19 vaccines be brought to the limelight of discussion, especially now that there seem to be inadequate time to follow up with the trial participants before the emergency approval. Now that vaccination already kick started, how long will the vaccine protection last? From participant recruitment to FDA-emergency approval, the process of clinical trials of these vaccines took less than six months. Therefore, it is believed that there was no adequate follow-ups to answer this question. Similarly, there is no current available data to understand whether the vaccines will require booster shots and the perfect time these might be expected.

Besides, the main goal of COVID-19 vaccines is to prevent personal infection. Then, will the vaccinated individuals still prevent the spread of SARS-CoV-2 virus to non-vaccinated individuals? Even with the high level of assurance being provided by the vaccine companies regarding their efficacies (especially the mRNA vaccines) against all forms of SARS-CoV-2 mutant strains, it remains to be acknowledged whether the vaccinated individuals can still spread the infection or not. While in the present situations, it may be virtually impossible to vaccinate everyone due to the logistic and economic reasons, this question demands immediate answer in containment operations.

In addition, the available vaccines data did not provide information regarding effectiveness of the vaccines in specific groups of people such as- asymptomatics, immunocompromised, previously infected individuals, paediatrics, pregnant and breastfeeding women, among many others. It is important to note that "efficacy" in clinical trials is not tantamount to "effectiveness" in clinical applications to all population groups. As at the time of writing this

report, none of the clinical trials have answered questions regarding these specific individuals, yet they were so listed in their exclusion criteria in clinical trial statement [77].

Furthermore, with the euphoria of arrival of the first COVID-19 vaccines, the virus seems to continue 're-strategizing' its battle with emergence of new mutant strains, rapidly spreading and affecting younger populations [78]. Now that we have emergency vaccine available, can the people infected with the new variants (such as UK- 20B/501Y.V1 and South African-20C/501Y.V2 strains) be protected? The answers we seek to these questions would be very germane to human safety and in addressing the global threats of COVID-19 disease that has affected socioeconomic wellbeing in many parts of the world.

76. U.S Food and Drug Administration. Emergency preparedness and response. Emergency authorization. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization. (accessed 04 January 2021).

77. ClinicalTrials.gov; US National Library of Medicine. Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals. Identifier: NCT04368728, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04368728. (Accessed 04 January 2021).

78. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L. Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: Insights from linking epidemiological and genetic data. PrePrint, 2020. https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-42-sars-cov-2-variant/. (Accessed 04 January 2021).

4th Editorial decision
23-Jan-2021

Ref.: Ms. No. JCTRes-D-20-00121R3
Addressing the Global Surge of COVID-19 Cases: Insights from Diagnostics, Improved Treatment Strategies, Vaccine Development and Application
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.

Journal of Clinical and Translational Research
Peer review process file 07.202102.002

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: