Dear Dr. Chen,

I write with some good news about your paper. We sent it for external peer review on a fast track basis and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, and hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting. We are looking forward to reading the revised version and making a final decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Sincerely,

Elizabeth Loder, MD, MPH

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/bmj?URL_MASK=8f7326276522407bb8d35fc57dc17f26

**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Present: Elizabeth Loder (chair); Gary Collins (statistician); John Fletcher; Wim Weber; Tiago Villanueva; David Ludwig; Joseph Ross

Decision: Request revisions before final decision

* We felt this provides useful information about the potential infectivity of various bodily fluids and types of patients. It seems to be the first that includes serum and stool samples. This may have implications for infection control measures such as the duration of quarantine.

* We were disappointed that you did not measure viral presence from all sources in all patients at each time period. This is a major limitation and should be acknowledged. Everyone eventually had a respiratory sample examined, but < 50% in the 1st week after admission; nearly everyone had serum, but < 33% in the 1st week. But 1 in 8 did not have a stool sample, nearly 1 in 3 were missing a urine sample (and the urine sample numbers stratified by mild and severe do not add up).
* We note that you speculate about which source is "best" for diagnosing the virus (which this study does not examine) and suggest that antivirals might be effective (which this study also does not examine). We would like you to remove these speculative comments.

* We agree with the reviewer who would like data on immunosuppressive drugs, anti-inflammatory medications, and steroid use. The timing and types of drugs used must affect the interpretation of viral load and shedding times. Severe patients were more likely to be on steroids and have higher viral load; which came first? If you can't describe and analyse this in more detail then you should discuss this more.

* Please provide a definition for "mild" and "severe" disease.

* What proportion of respiratory samples were of sputum vs saliva? This distinction would be important in contrasting viral load with other specimen types. If more severe cases have a more productive cough (or samples were more likely to be obtained by bronchio-alveolar lavage) the higher viral load per ml may reflect better sampling of bronchial contents. That is, in people with a dry cough, if a sample of sputum is difficult to obtain and is mostly saliva then that could substantially underestimate the true respiratory load.

* How were the patients sampled? Were they consecutive patients? Some more information on this and eligibility to be in the cohort would be useful.

* Table 3 needs needs better explanation. 'Underlying disease' is a mixed bag of diseases (Table 1). Presumably 'sex' relates to Male sex in that model?

* Our statistician noted that the modelling here is quite simple and that it is unlikely that age is linear. He was not convinced of the usefulness of this analysis and suggests that you omit it.

* Figures 2 and 4 – the raw data points could/should be presented as per Figure 1.

* The term "multivariate" should be multivariable.

* Important: We need a better description of the timecourse and outcome for these patients since the main measure of interest is time and viral shedding. A study flow chart would help as well as a table of outcomes (dead, discharged, in hospital).
  i) 16 patients were still in hospital at the time of writing
  ii) 30 patients were in ITU at some time but the number of deaths is not reported nor how viral load and timing was dealt with in these patients
  iii) were patients discharged when clinically stable, even if still shedding virus, or were they kept until clear (even if well)? How many?

* There was a recent paper in Gastroenterology that talked about fecal oral transmission so the stool viral load is quite interesting and helps not only clinicians understand methods of possible spread but will help scientists possibly understand better ways to develop kits and mechanisms to test and transmission and might aid public health agencies in understanding how to test. Might patients be able to just drop off a stool sample?

* We thought you might want to mention and discuss these recent papers:
  SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.
Zou L1, Ruan F2, Huang M3, Liang L1, Huang H2, Hong Z3, Yu J1, Kang M1, Song Y1, Xia J3, Guo Q1, Song T1, He J1, Yen HL4, Peiris M4, Wu J5 with respiratory samples from 17 patients.

And there is one paper on MedRxiv with 96 patients:
https://www.medrxiv.org/content/10.1101/2020.03.15.20036707v2
Reviewer: 1

Major comments:

- While this study is extremely timely and provides very useful data, some additional clarifications would help to make it maximally useful to the global community.
- In this study, did you collect any specimens from patients following discharge? Or only during their hospitalization? Discharged patients could bias your analysis, if at the later time points you'd only be collecting specimens from patients who remain hospitalized, overinflating the estimates of viral load and duration at the later time points. This point should be discussed/explored if patients were in fact discharged and therefore no longer eligible for inclusion in this analysis.
- To guide interpretation of the results, the manuscript should include a more thorough description of the distribution of when various specimens were taken in relation to symptom onset. Table 2 includes some of this information, but a graph or even median (IQR)s would be helpful.

More detailed comments:

Overall:

- Should use consistent terminology: viral load vs. virus load
- This article would benefit for a thorough English-language edit

Title:

- Would be nice to indicate the dates/place in the title, so readers can quickly place the setting.

Abstract:

- Line 56: can you give the exact number of samples collected?
- Lines 56-57: the words "and detection" seem unnecessary
- Line 57: RNA should be spelled out. Should also indicate method used for assessing RNA viral load.
- I would swap the second and third sentences of the 'main outcome measures' section. You need to scribe how clinical data was collected before analyzing the relationship between the clinical data and viral load.
- Results: did any patients have SARS-CoV-2 detected in non-respiratory specimens, but the respiratory sample was negative?
- Line 62: should indicate that by 'respiratory specimens', you are referring to sputum and saliva specimens.
- Line 63: should mention that only 1 patient had a positive urine sample
- To help interpret the duration of virus detection in various samples, can you indicate what you are considering symptom onset as day 0?
- Can you also indicate the distribution of time in which specimens were collected? Based on the time window of Jan 19-Mar 12, I’m guessing the maximum possible duration is 53 days, but would be good to see the median (IQR).
- Line 66: how were 'severe' and 'mild' defined? This classification should be mentioned in the methods.
- Lines 68-69: when you refer to 'peaks', are you referring to only respiratory specimens (as hinted in the Abstract conclusion), or to any type of specimen?
- Line 70: should indicate the direction of the correlations between age/sex and viral duration. What category of age and sex had longer viral duration?
- Lines 72-73: These results don't directly indicate that 'respiratory samples are still the most effective', as the analysis was limited to patients with positive respiratory samples.

Introduction:

- Line 106: would suggest updating case counts/deaths at the time of publication.
- Line 108: need to define ARDS
- Line 109: did all patients who developed ARDS/pneumonia die? If not, should change phrasing.
- Line 111: should be 'tract', not 'track'
• Line 114: should probably define COVID-19 in the first paragraph of the intro

Methods:
• Line 125: is this really a cross-sectional study, as you have repeated samples over time from individual patients? Seems more like a cohort to me.
• Line 133: It seems like respiratory specimens were limited to sputum and saliva samples. No oropharyngeal swabs or nasopharyngeal swabs were included, correct?
• Lines 139-143: This info belongs better in Results.
• Lines 150-151: do you mean “specimens with repeated results of Ct values >28 were considered NEGATIVE”?
• Line 161: can you include the definitions of Mild and Severe that you use in this analysis, for easy reference?
• Line 166: ‘patients who test negative for 2 consecutive days’ – does this include testing of any specimen? Or only respiratory specimens?
• Lines 167-169: this sentence goes better in the Results.
• Line 171: I don’t see that standard deviations are actually used in this manuscript.
• Line 177: can you include a reference for the loess method?
• Lines 178-179: ‘only the patients whose viral load were monitored more than five times were included’ – meaning 5 viral loads from a specific specimen type, or 5 viral loads from any type of specimen?

Results
• Lines 191-192: do you mean ’29 (30.2%) >5 days after symptom onset’?
• As mentioned in the Abstract comments, would be helpful to indicate the distribution of time after disease onset in which these specimens were collected.
• Lines 203-204: “which was not reflected in stool” – do you mean that there was no difference in the rate of detection in stool samples between severe vs. mild patients? Please clarify.
• Lines 204-205: could explicitly state that only 1 urine sample was positive.
• Line 214: should update subtitle to include that you looked at the correlation between viral load and specimen type as well. Should also explicitly state in the Methods that you performed this aspect of the analysis.
• Lines 221-225: should be clear that you are referring to viral load in respiratory specimens.
• Lines 224: based on the Figure, consider rephrasing to: “in the severe group, the viral load continued to be high during the third and fourth weeks following disease onset (Fig.3 Red line)” – this phrasing is more clear and seems to accurately reflect the figure.
• Lines 225-226: based on the Figure, consider rephrasing to: “The viral load of fecal samples was highest during the third and fourth weeks following disease onset”.
• Lines 229-230: should indicate the direction of the correlations between age/sex and viral duration. What category of age and sex had longer viral duration?
• Lines 233-234: should clarify that you mean 60 YEARS.

Discussion:
• Line 236: should say ‘COVID-19’
• Lines 239-242: This statement is not an accurate conclusion from this analysis as currently written, as the analysis was limited to patients with positive respiratory samples.
• Lines 244-245: does this sentence specifically refer to viral shedding via respiratory specimens?
• Lines 247-248: this sentences conflates the concepts of virus detection duration and viral load. Please rephrase.
• Lines 268: strain isolation wasn’t mentioned in the methods or results, so seems out of place here.
• Line 281: bone marrow specimens were not mentioned in the methods or results, so seem out of place here.
• Line 295: again, not sure this is considered a cross-sectional analysis.
• Lines 305-306: clarify whether you are referring specifically to respiratory specimens here. Also, in your study, did you collect any specimens from patients following discharge? If not, it’s hard to compare your results to this study.

Tables
• Table 1:
It's interesting that patients infected in Wuhan were more likely to have severe disease. This could be discussed in the Results.

Did any of the 96 patients die? If so, can you include that info in Table 1 and the Results?

- **Table 2:**
  - The heading over columns 4-7 should be clarified. A possibility: "SARS-CoV-2 detection by week since symptom onset"

- **Table 3:**
  - Can you clarify the ‘Age’ and ‘sex’ variables? How were these included in the model? Ideally, this table should specify something like ‘>60 years vs. ≤60 years’ and ‘Male sex’. It would be good to include the definitions used for these variables in the Methods as well.

**Figures**
- **Figure 1:**
  - Title should specify “Duration of SARS-CoV-2 DETECTION in different sample types”
- **Figure 2:**
  - Overall figure title is not appropriate, as that only describes Panel A. Either remove overall figure title, or come up with more comprehensive figure title.
- **Figure 4:**
  - Y-axes need titles

Additional Questions:
- The **BMJ** uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The **BMJ**, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

**Please confirm that you understand and consent to the above terms and conditions.:**
I consent to the publication of this review

Please enter your name: Heidi Soeters

Job Title: Epidemiologist

Institution: U.S. Centers for Disease Control and Prevention

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No
Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <a href="http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests" target="_new">(please see BMJ policy)</a> please declare them here:

Reviewer: 2

Comments:
The manuscript under revision is well executed and well written
During the current pandemic articles on cohorts of patients from countries that have the most experience in battling this disease are worthwhile
And the main message regarding the duration of viral shedding in mild and severe Covid 19 patients and the viral shedding in different excretions is clear and useful.
The statistical analysis is well executed and clearly described
I therefore regard this manuscript as potentially fit for publication

However, the main limitation of this manuscript is the limited information that is provided on medication used in the different patient groups
There was a very high usage of steroids and antiviral drugs, which both could have dramatic effects on viral dynamics and clinical outcome.
The authors do mention this in their limitation section, but in my view they need to include more data on the different drugs used in their results section.

Additional Questions:
<em>The BMJ</em> uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from <em>The BMJ</em>, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our <a href="https://www.bmj.com/about-bmj/resources-reviewers" target="_blank">peer review terms and conditions</a>. 
Please confirm that you understand and consent to the above terms and conditions.

I consent to the publication of this review.

Please enter your name: Roos Barth

Job Title: Internal medicine and infectious diseases specialist

Institution: University Medical Centre Utrecht

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?:

If you have any competing interests please declare them here:

[please see BMJ policy]