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Subject: BMJ - Decision on Manuscript ID BMJ-2020-054741

Body:

06-Feb-2020

BMJ-2020-054741 entitled "Clinical findings of second-generation patients with 2019 novel coronavirus: a multicenter, retrospective, observational study"

Dear Dr. Li,

Thank you for sending us your paper for fast track assessment. We sent it for external peer review and discussed it at our manuscript committee meeting today. We are pleased to offer publication in the BMJ if you are able to revise as we suggest below.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting and we are looking forward to reading the revised version. In view of the rapidly evolving situation this offer of publication is conditional on rapid turnaround of the revision by yourselves. If there is a delay in returning your manuscript of more than a week we may have to reconsider our offer to publish.

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.

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****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.

Members of the committee were: Elizabeth Loder (chair); Jon Deeks (statistician); John Fletcher; David Ludwig; Tiago Villanueva; Tim Feeney; Joseph Ross; Shivali Fulchand; Helen MacDonald

Decision: Put points

Detailed comments from the meeting:

1. Thank you for sending us your interesting case series at this early stage in the outbreak of 2019nCoV. We would like to proceed with fast track publication and ask that you revise your manuscript as quickly as possible.
2. We think your study is best characterised as a case series rather than an observational study. Please alter the title accordingly.
3. Please give more attention to describing how you assessed the timing of exposure and onset of symptoms as this will influence the reliability of the estimates of incubation period.
4. Please describe the criteria for inclusion into your study. We understand that these are cases admitted to hospital but was there an increased vigilance and tendency to admit suspected cases to an institution in order to monitor this new disease? If that is the case then it may explain the milder spectrum of disease compared to the initial cases before more active surveillance.
5. We understand that this infection may be relatively prolonged and therefore it may be a little early to comment on the absence of deaths. Similarly until everyone has been discharged it is not possible to comment on the length of stay. Please alter your conclusions accordingly.
6. We note the geographical separation of your hospital from the original source of the outbreak. Can you comment on why so many cases have been seen in your area rather than other cities and regions in China?
7. Without information on the denominator (number of people exposed) it is not possible to comment with much certainty about the transmissibility of the infection. Please reconsider some of your statements about this.
8. We agree with the reviewers that more clinical information describing the cases would be very helpful. At the moment your summaries are very high level and "epidemiological". Please include as much of the information suggested by the reviewers as possible.
9. Since you are reporting a case series we do not think it necessary to apply statistical tests to any descriptions or comparisons made.
10. Please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

Li et al. described patients with laboratory-confirmed infection 2019-nCoV in Zhejiang province. None of these patients have exposure to Huanan Seafood Market but all have exposure to infected patients. Furthermore, these patients either have long-term residence in Wuhan or short-term trip to Wuhan. This paper provided more information about the clinical features of 2019-nCoV infected patients. However, several important limitations should be addressed for this paper. 1) Human transmission was inferred from the study by lack of exposure to the Huanan Seafood Market from all patients, but lack of exposure history to the Market is not sufficient for proving person-to-person transmission, especially under the condition that all the patients have been to Wuhan and that the source for 2019-nCoV was still not clear. 2) The authors did not provide clear definition of second-generation and how all these patients enrolled in the study were identified as second-generation. 3) The definition

of incubation period was not clearly provided. The authors mentioned in Result section patients who had short term trip to Wuhan were included to calculate the incubation period, but the numbers provided in the table were for all patients enrolled in the study.4) Tables were not informative as no important comparison was made (also no p values). Other points are addressed as follows:

Major

1. Abstract, Line 64: How was the time point for infection exposure identified for patients who either have long-term residence in Wuhan or short-term trip to Wuhan? This should be clarified.
2. Methods: The word "course" was ambiguous. Does this mean length of hospitalization or the time since illness onset? Please clarify.
3. Methods: The authors included 62 cases in this study, but mentioned "a large number of patients showed up" so they just collected "most but not all" patients. Is there a justification for choosing these 62 cases? Are they the earliest cases? Or please indicate a time period for collecting cases.
4. Methods-Statistical analysis: In the research conducted by Huang et al, the median time from onset of symptoms to ICU admission was 10.5 days. This number was calculated among those with ICU admission. However, among 62 patients enrolled in this study, only one patient was admitted to ICU. Nearly all of the patients are still in hospitalization when the authors submitted the paper. This means patients will gradually move from duration time <10d to duration time >10d. The duration of hospitalization cannot reflect the disease severity and is not a good classification variable at this specific time point.
5. Methods-Statistical analysis: It is not reasonable to make comparisons between all the patients enrolled in the study and patients with course longer than 10 days, as the latter ones were part of patients included in the study. The authors should make comparisons between those with and without course longer than 10 days.
6. Methods-Statistical analysis: The authors only gave brief description of different characteristics. Statistical analysis should be performed with statistics calculated and p values listed in each table.
7. Results-Lines 155-156: Why only patients who had short term trip to Wuhan were included to calculate the incubation period? How was the time point for infection exposure identified? In lines 171-172, the incubation period was calculated for all the 62 patients. These were inconsistent through the article.
8. Discussion: "According to our data, none of the infection cases in Zhejiang had ever been exposed to the Huanan seafood marker, all the patients were infected by human transmission." This sentence should be revised. Without exposure to Huanan Seafood Market is not the sufficient conditions of human to human transmission as the source of infection is still not clear.
9. Discussion: Chen et al. published their data on 99 cases of 2019-nCoV patients on Jan 30, 2020 in the Lancet. Clinical characteristics from these patients should also be discussed, apart from the 41 patients in Huang et al.'s cohort.
10. Conclusion: Line 254 "The 2019-nCoV could be easily transmitted from human to human." This sentence should be revised. A study focusing on clinical features of admitted patients shall not reveal the transmission status. Please refer to the epidemiological study published by Li et al on January 30th in New England Journal Medicine.

11. Table 1-3: No comparison was made with only the descriptive values listed. These tables are not informative.

12. Table 4: Information listed in the table can be found in Table 1-3. Descriptive comparison between results from this study and that from Dr. Cao should be addressed only in discussion section but not in a separate table.

13. Moderate linguistic (English) corrections are desirable. Present version has some punctuation, grammatical and typological sentence framing issues which should be taken care of by the authors.

Minor

1. Line 50: Grammar mistake: "covered", "are located in", "parts".
2. Line 52: please be specific about the date.
3. Line 63: "Few" patients, not "rare". Do you mean shortness of breath at illness onset, or during hospital treatment? Same for line 176 and 182.
4. Line 67: "secondary infection" should be replaced with "second-generation"?
5. Line 79: "most" is better than "nearly all", because only 66% had been exposed to the market in this cohort.
6. Line 86: This number has already surpassed the sum for SARS-CoV and MERS-CoV, please update. Same for line 202.
7. Line 88-89: "the clinical investigation of patients was still limited in the literature". Please clarify what is "limited in the literature". Do you mean "number of published studies is limited"?
8. Line 97-98: Should be reference #9. Please specify what are defined as imported case?
9. Line 100: What are "these people"? Please specify.
10. Line 109: What is the definition for suspected case? Does travel or contact history count as a mandatory criterion for suspected case? Should be "especially" (line 110).
11. Line 125: For laboratory confirmation, what samples did you use for RT-PCR? Nasopharyngeal swabs or BALF?
12. Line 128: Please specify what is "and so on"? Any tests for other common respiratory pathogens?
13. Line 128: Most patients, without the "of".
14. Line 129: What is "Lopina veletonavir"? I assume it is "Lopinavir/Ritonavir".
15. Line 132: Please provide dosage for corticosteroid therapy and IVIG.
16. Line 134: What is the unit of CRP?
17. Line 136: Please clarify the definition of "2019-nCoV clearance".
18. Line 156, Line 166: Please avoid the word "select".
19. Line 164: Is 1.6% the percentage for COPD or diabetes? Same for line 168.
20. Line 165, Line 169: What is the meaning of "associated with" familial clusters? Did the authors mean relatives of the 21 patients were also reported to be infected by 2019-nCoV? Were the relatives included in this cohort?
21. Line 177: "... course over 10 days. We found" should be revised to "... course over 10 days, we found".
22. Line 185: "The D-dimer level was higher (median D-dimer level 0.2 mg/L [IQR 0.2-0.5])." Higher than what? No comparison was made.
23. Line 193: "patient transferred" should be revised to "patient was transferred".
24. Line 194: By antiviral, is it lopinavir or oseltamivir?
25. Line 197: "One patient has". Singular form.
26. Line 206: Suggest adding "early" before "2019-nCoV cases in Wuhan". Chen et al. has reported clinical features for another 99 cases in Wuhan (the Lancet) who had similar features.
27. Line 211-212: Please clarify "air prevention". Do you mean "airborne transmission precaution"?
28. Line 217 "developed to" → "developed"

29. Line 218 "admitted"→"were admitted"
30. Line 219: "Fewer" patients.
31. Line 230: Please clarify "not much". Addressing the difference in antiviral therapy, patients in Huang et al. paper did not use lopinavir and many were given empirical oseltamivir.
32. Line 236 "Given that most infections in Zhejiang were secondary-generation infections," This sentence contradicted with the Line 207-209, where you stated all patients were infected by human transmission. Please clarify.

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Job Title: Doctor

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Reviewer: 2

Recommendation:

Comments:

This is a very important manuscript as it deals with the outbreak in Zhejiang which is the second largest outbreak of the novel coronavirus outside of Wuhan. Although no deaths have been reported from Zhejiang, the size of the outbreak is huge with close to 600 reported cases to date. Also the measures taken by the province are drastic with the total shutdown of Wenzhou. As such the manuscript is timely but there are several issues which need to be addressed. They include

Major

- 1) The rationale for using a 10 day cutoff to divide the cohort is not clear. In the Huang et al reference cited to justify this, the median time to dyspnea was 8 days and the median time to ARDS was 9 days, ICU admission 10.5 days. It would make more sense to look at the cohort as a whole and provide some data on the duration of illness for the whole cohort.
- 2) The way the results are presented also does not make sense. Patients in the tables are essentially counted twice – first in the whole cohort and then in the “10 day cohort” Given the fact that patients were essentially kept in hospital until they were presumably PCR negative for the coronavirus, what the two groups appear to represent are those who presented earlier in the epidemic in Zhejiang vs those who presented later in the epidemic. This should be emphasized and perhaps the whole cohort analysed together.
- 3) It is not clear from recently published reports (references 1,9 and 10) that “most of the patients had been to the local seafood market as stated in lines 72 and 73. Also the viral genomes are not closely related to snake genomes!
- 4) The figure in line 76 is misleading as the total number of cases of SARS and MERS appear to be added up although the references only refer to MERS. It would be clearer to separate MERS from SARS and report cases and deaths from both
- 5) The statement in line 82 that the virus is mainly transmitted from animals to humans is also not supported by any data. Although the virus is related to a bat virus, to date, there has been no animal shown to be infected with this virus. Perhaps the authors could say instead “The virus is believed to have been transmitted from animals”
- 6) The case definition needs to be provided. There is a citation to reference 1 which does not have a clinical case definition but has only two cases described without a case definition.
- 7) While the drug “Lopinavir-ritonavir” may be available in China as a variant of lopinavir-ritonavir, some reference needs to be provided to help understand its pharmacology (line 129) similarly for inhaled interferon 1B
- 8) Details also should be provided for steroids, “gamma globulin” and probiotics used in the patients. Perhaps an additional table could be used to list out the different treatment modalities used and the outcomes in simple terms such as number of days on oxygen therapy
- 9) It is not clear what is the difference between “long term residents” of Wuhan and “short term visitors” if all the study subjects lived in Zhejiang. Presumably all of the individuals studied had left Wuhan for Zhejiang at some point in time and the duration that they stayed in Wuhan might be considered a variable in estimating their

exposure to infected patients in Wuhan perhaps. That is unless the “long term residents” were people who fled Wuhan to avoid the lockdown and thus were more likely to be incubating the virus. This does not seem to be the case as the presumption is that all the infections were acquired in Wuhan and the incubation period is calculated from the time the short term visitors left the city.

10) Line 165 includes the intriguing figure of one third of the cases associated with family clusters. More information is needed on this – did whole families travel to Wuhan and get infected or were there index cases who travelled who infected others in their families?

11) There are contradictions in the numbers of individuals in the family clusters – line 165 says that overall, it was more than one third 21/62 but of those who had been infected earlier – i.e. hospitalised for more than 10 days, it was “less than one third” but reported as 21/33 (line 169). This may be a typo but it is interesting if indeed the first cohort were more likely to be travellers while the more recently infected were locally acquired in Zhejiang from family members. This needs to be clarified.

12) Line 184 describes leukopenia as a feature of the patients but it was apparently seen in only a third so it may not be the case

13) Line 188 states that all patients had abnormal chest x-rays or CT scans. Then line 192 states that one patient did not have pneumonia. It is not clear what were the findings in the patient without pneumonia

14) Line 196 has the most intriguing statement that based on criteria of 3 days of stability and clearance of virus, only one of 62 patients was able to be discharged. This should be clarified – did these patients with apparently mild disease continue shedding virus? Or were they still unstable? This should be clarified

15) The main conclusions are not clearly supported by the data. The mildness of the infection cannot be confirmed without more data. With the family clusters, it is not clear if these are just secondary infections or are they tertiary infections. Person to person transmission has been established since the beginning of the infection as there is still no evidence of an animal source.

Minor

1) The grammar needs some work – for example in the objectives, patients are not imported. The disease is imported with patients who move. Terms such as “Rare of patients developed shortness of breath” should be re-written as “It was rare for patients to develop shortness of breath”

2) The case report form should be provided in the supplementary material and ideally this should conform to standard case reporting

Additional Questions:

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If you have any competing interests [please declare them here](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests): I have received research grants paid to my institution from Sanofi-Pasteur, GSK, Roche, Johnson and Johnson in the last three years

Reviewer: 3

Recommendation:

Comments:

This is a retrospective observational study describing clinical findings in patients infected with the 2019-nCoV in the Zhejiang province, which reports the greater toll in China after the Hubei province. Available data in the literature on clinical course of patients infected by the 2019-nCoV are still scarce, and gathering clinical findings is of high interest.

In general, the manuscript would benefit from thorough language editing.

The study has been approved by local ethics committee, and the authors clearly specify that informed consent has been waived because of the urgent need to collect data on a new pathogen.

Some shortcomings needs to be addressed.

Major concerns:

Zhejiang is the province where most of the cases are reported after Hubei, where 829 confirmed patients were reported as of Feb 3, 2020. The authors present here important clinical data. However, only 33 of the patients they describe have a follow-up of more than 10 days after onset of disease, and the length of the disease is not specified. As the author stated, Huang et al. reported in the Lancet that the novel 2019 pneumonia is a long disease, and that complications (and ICU admissions) appear in median 10 days after onset of symptoms. Most of the patients described here are still hospitalized at the time of the writing, and their final outcome is still unknown. The authors state that in their cohort, patients present with milder disease than what has been described from Wuhan, based on the fact that only one on 33 patient with symptoms lasting more than 10 days presented with dyspnea. However, all but one of the described patients presented with imaging confirmed pneumonia, and no data is available on pulse oximetry or on the need for supplemental oxygen. It would be of great interest to have data presenting the whole course of disease and the outcome of the patients, in order to be able to conclude that the disease is less severe than what has been observed in Wuhan. The authors should specify which clinical material was used to confirm the diagnosis, and what were the results of the RT-PCR tests in the different specimen tested, if available.

The authors report temperature and respiratory rate of the patients. Are there any data on pulse oximetry or blood pressure available? This is important since the authors state that patients with a saturation below 93% in ambient air have been treated with investigational therapeutics, and since this is a marker of the severity of a lung disease.

Among administered treatment, could the authors specify how many patients benefited from supplementary oxygen therapy?

Minor concerns:

The authors state in the design of the study that data come from multiple centers. Could the authors specify (line 111) how many "designated hospitals" participated to the study, and which type of center it involves (tertiary, secondary, primary).

Introduction:

- Line 73: the fact that snakes are intermediate hosts of this novel coronavirus is highly criticized in the scientific community. There is no current proof that coronaviruses can infect species other than mammal and Aves, and I would suggest to remove the word "snake" to avoid any further misunderstanding.
- Lines 73 to 76: The statement that 2019-nCoV is "very similar" to SARS-CoV and MERS-CoV should be revised: all of those viruses are within the same genus of the subfamily Orthocoronavirinae in the family Coronaviridae. 2019-nCoV is like SARS-CoV, a member of the subgenus Sarbecovirus (Beta-CoV lineage B), with which it shares more than 79% of its sequence, but is more distant to MERS-CoV, which belongs to the Merbecovirus subgenus (only 50% homology with nCoV). A reference on SARS should be added. Total cases of MERS and SARS shouldn't be added, since they display different case fatality rates.

Methods:

- Could the authors share their standardized case-report form as supplementary material?
- Line 125: "... real-time RT-PCR..." please correct.
- Line 128 "and so on": please specify which test has been performed.
- Line 129: "lopina veltonavir" please use the international nonproprietary name
- Lines 132-133: please specify the dose and the molecule used for each treatment
- Please specify which antibiotic has been administered
- Line 135-136: only confirmed patients can clear the virus. The sentence should be rephrased for more clarity.
- Not being an epidemiologist, I won't extend on the statistical analysis.

Results:

- Characteristics of the patients: could the authors specify the age of the two younger patients? Are there any children below 5 years-old?
- Line 155-156: the method of calculation of the incubation period should be described in the methods section
- When presenting the data in the table, clinical data such as temperature and respiratory rate should be displayed next to each other for more clarity, then followed by symptoms.
- Could the authors specify if patients presented with upper respiratory symptoms?
- Could the authors specify the normal laboratory values range in table 2?
- lines 185-186: "the D-dimer level were higher": this sentence should be rephrased for more clarity.

Discussion:

- Could the authors specify what they mean by "air prevention"?
- The authors should discuss the fact that antiviral therapy, gamma globulins and steroids were administered within an uncontrolled study, and that no conclusion can be drawn on their effect.

In a nutshell, gathering clinical data during an outbreak of a new pathogen is of high importance. The manuscript should benefit from a revision before publication. If data are available at the time of the revision and if the authors chose to review their paper, the paper could be updated with new available data on the outcome of the patients in their cohort.

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