Author's response to reviews

Title: Clinical Characteristics of the Autumn-Winter Type Scrub Typhus Cases in South of Shandong Province, Northern China

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Author's response to reviews: see over
RE: MS: 3905916322295992

“Clinical Characteristics of the Autumn-Winter Type Scrub Typhus Cases in South of Shandong Province, Northern China” by Yunxi Liu et al.

Dear Dr. Todd,

We are pleased to re-submit the enclosed manuscript for your consideration for publication in the BMC Infectious Disease. The title of our (revised) manuscript is: “Clinical Characteristics of the Autumn-Winter Type Scrub Typhus Cases in South of Shandong Province, Northern China”.

We greatly appreciate the three reviewers’ constructive and, in general, favorable comments on our manuscript submitted previously. Following their suggestions, we have revised the paper accordingly. Enclosed are a point-by-point response to reviewers’ comments and the revised manuscript.

We thank you for considering the manuscript and look forward to hearing from you.

Sincerely,

Yunxi Liu, MD, PhD

Enclosures:

1. A point-by-point response sheet.
2. Revised manuscript (clean version).
Response to reviewers’ comments

**Manuscript title:** “Clinical Characteristics of the Autumn-Winter Type Scrub Typhus Cases in South of Shandong Province, Northern China”.

**General Note:**

1. In the revised manuscript we have specifically elaborated the differences between the summer and the autumn-winter types. In particular, we added Table 6 in Discussion section summarizing causative strains features relating to the clinical features, geographical distributions of the patients and vectors. Meanwhile, further related references are added in both Introduction and Discussion sections.
2. We have revised the map by adding locations of the five townships where the study was conducted. Unfortunately, specific information on case distribution within each village of the study area were unavailable, we compromised it by adding a township distribution map.

**Assistant Editor:**

1. Please remove the following from your Title Page:
   - LRH: Liu and others
   - RRH: Characteristics of the autumn-winter type scrub typhus cases
   - *Yun-xi Liu, Dan Feng are equal contributors.

**R:** Done as suggested.

2. Your abstract is much too long. BMC imposes a 350-word limit on the abstracts published in BMC-series articles. Please re-write your abstract so that it contains fewer than 350-words. At the moment your abstract is 476 words long.

**R:** Done as suggested. In light of the reviewer's comments, we have rewritten our abstract so that it contains 347 words.

3. Please re-name your "Materials and Methods" section as "Methods".

**R:** Done as suggested.

4. Please include a specific "Conclusions" section. This section should follow your "Discussion" section.

**R:** We have added a specific "Conclusions" section, following "Discussion" section in the revised manuscript according to the reviewer’s suggestion (Page 20, 2nd paragraph).

**Reviewer 1:**

29. The distribution map of the cases in the study areas will be highly attracted the readers of the journal. Please add the information.
R: Done as suggested.
RR: I meant the distribution map of the cases in the study areas, not the study areas.
R: We have added distribution map of the cases in the study areas in Figure 1 in the revised manuscript according to the reviewer’s suggestion.

34. (Page 8 line 16) In "data collection", it stated activities as the time of infection. Please define the time of infection. for example. ? time before the day of onset.
R: We agreed...........1-3 weeks prior to onset of symptoms.
RR: please explain that 1-3 weeks is the incubation period of this autumn-winter type scrub typhus.
R: We have explained that 1-3 weeks is the incubation period of this autumn-winter type scrub typhus in the revised manuscript (Page 9, first paragraph, lines 1--2).

Reviewer 2:
Major Compulsory Revisions
The authors reported clinical characteristics of scrub typhus cases in China. This report showed the cases in Shandong Province and they are the Autumn-Winter Type. It would be better to describe the previous Summer type and then summarize the difference between the Summer and the Autumn-Winter types if the authors focus on the Autumn-Winter Types. I think that the revised version still does not describe the difference or highlight specific features of each type clearly, especially about infected or causative strains relating to the clinical features, geographical distributions of the patients and vectors.

As the authors suggested, in Japan and Korea; the neighbor countries having very similar climates, Autumn-Winter type is very common and well described in some reports. I recommend that the authors should refer some more epidemiological reports about this type of these countries.
R: In Background section, we have added the study results of the serotypes and genotypes of the O. tsutsugamushi isolates which caused summer type scrub typhus in southern China (Page 6, 2nd paragraph, lines 8--12), as well as those of the O. tsutsugamushi isolates which caused the autumn-winter type scrub typhus in northern China (Page 7, 2nd paragraph, lines 11--15). The virulence of O. tsutsugamushi isolates, clinical features and complications of the autumn-winter type scrub typhus were also supplied (Page 7, first paragraph, lines 1--3).

In Discussion section (Page 14, 2nd paragraph; Page 15, first paragraph), the key differences between “summer type” and “autumn-winter type” scrub typhus obtained from previous reports and the present study in China were described and then summarized in Table 6. Table 6 summarized the differences between the “summer type” and “autumn-winter type” scrub typhus in detail, including seasonal distribution of cases, geographical distributions, key hosts and vectors, virulence of the O. tsutsugamushi isolates, key serotypes and genotypes of the O. tsutsugamushi isolates, and clinical features and complications.
According to the reviewer’s suggestion, we also compared the epidemiological features of autumn-winter type scrub typhus in northern China with that of scrub typhus in Japan and Korea in Discussion section (Page 14, 2nd paragraph, lines 3--9; Page 15, first paragraph, 1--4).

**Minor Revisions**

**[Abstract]**

1. P5 L5 and 15

Lymphadenopathy was observed in 60.6% of cases and the authors concluded it was typical major symptoms. I wonder 60.6% is high or not.

*R:* We agree with the reviewer’s comment. We have deleted the statement that “lymphadenopathy was the typical major symptoms” in revision to reduced the confusion.

2. P5 in Conclusion

Most parts described common clinical features of scrub typhus, not only in Autumn-Winter type. It would helpful for readers to highlight the clearly.

*R:* We have revised the Conclusion section according to the reviewer’s suggestion. In Conclusion section in the revised manuscript, we described the key differences between autumn-winter type and summer type scrub typhus in China.

3. P5 in conclusion

As far as I know, CRP, liver enzyme elevations are also typical major symptoms of scrub typhus. Was there no important information in this type?

*R:* We agree with the reviewer’s comments that elevations of C-reacting protein (CRP) and liver enzymes are also typical major symptoms. Because of economic reasons, most farmer cases especially adult cases were unwilling to pay for any more biochemical tests than routine hematological examinations. So unfortunately information about CRP and liver enzymes could not be provided in current study.

**[Background]**

4. P6

There is a few information about clinical characteristics, infected strains and epidemiological aspects of Summer type although the authors discussed those of Autumn-Winter type in this article. I think that it would be greatly helpful for readers to describe them.

*R:* We agree with the reviewer’s comments. In Background section, we have added the study results of the serotypes and genotypes of the O. tsutsugamushi isolates which caused summer type scrub typhus in southern China (Page 6, 2nd paragraph, lines 8--12), as well as those of the O. tsutsugamushi isolates which caused the
autumn-winter type scrub typhus in northern China (Page 7, 2nd paragraph, lines 11--15). The virulence of O. tsutsugamushi isolates, clinical features and complications of the autumn-winter type scrub typhus were also supplied (Page 7, first paragraph, lines 1--3).

In Discussion section (Page 14, 2nd paragraph; Page 15, first paragraph), the key differences between “summer type” and “autumn-winter type” scrub typhus obtained from previous reports and the present study in China were described and then summarized in Table 6. Table 6 summarized the differences between the “summer type” and “autumn-winter type” scrub typhus in detail, including seasonal distribution of cases, geographical distributions, key hosts and vectors, virulence of the O. tsutsugamushi isolates, key serotypes and genotypes of the O. tsutsugamushi isolates, and clinical features and complications.

[Material and Methods]

5. P8
Is there any difference between yearly cases?
R: The case numbers were relatively higher in 1995, 1996, 1997, and 2000 than in other years. The clinical features of cases were compared between yearly cases, no significant differences were found.

6. P8
Why did you use Karp, Kato and Gilliam strains for IF? Are the causative strains in China? It would be better to comment about the causative strain types in China in the Background section if the authors show some data about it (Ex. In result section of PCR and RFLP)
R: In Background section, we have added the study results of the serotypes and genotypes of the O. tsutsugamushi isolates which caused summer type scrub typhus in southern China (Page 6, 2nd paragraph, lines 8--12), as well as those of the O. tsutsugamushi isolates which caused the autumn-winter type scrub typhus in northern China (Page 7, 2nd paragraph, lines 11--15).

Major serotypes of summer type scrub typhus in many areas of southern China were Karp, Gilliam, and Kato types. In China, genotypes of scrub typhus have not been systematically studied until recently. However, the genotyping results obtained in partial areas in Guangdong, Fujian, Hainan province of southern China revealed that Karp types were the key genotypes of summer type scrub typhus in these areas.

Although Gilliam types were identified by IFA as the key serotypes of autumn-winter type scrub typhus in many areas of northern China, the genotyping results acquired in Shandong, northern Jiangsu province in northern China showed that Kawasaki types were the key genotypes of this type of scrub typhus (the genotypes in other areas were not studied or undetermined).
Because Kawasaki strain was not available as antigen in China, we had to use Karp, Kato, and Gilliam strains as antigens for IFA.

[Discussion]

7. P13 I wonder why there are two peaks in Japan although one peak in China. This difference seems very interesting. It would be better to make this part of discussion more clearly.

**R:** In Japan, the patterns of a bimodal occurrence of cases were reported to relate to the activities of two different species of chigger mites. Cases occurred in the autumn-winter period in many areas were mainly due to L. scutellare, while those in the spring period in western Japan were caused primarily through L. pallidum.

We have added the description in Discussion section (Page 14, 2nd paragraph, line 13; Page 15, first paragraph, lines 1--4).

8. P14 maculopapular rashes, chills, … occurred more frequently. Is this related to the isolated strain, Kawasaki? It would be helpful for readers if some information of this strain were provided.

**R:** Maculopapular rashes, chills, … are the common clinical features of scrub typhus, and these features are not the unique features caused by Kawasaki strain.

We have provided some information about Kawasaki strain in Discussion section in the revised version (Page 19, 2nd paragraph, lines 1--8).

9. P16 Eschars distribution on body is very interesting. Especially there is difference between men and women. Is there any relation to their job styles?

**R:** Similar to many reports in China, our results showed more cases occurred in male (56%) than in female (44%). However, this was in contrast with that in Korea, where scrub typhus infections occurred more frequently in females than in males. This could be partly explained by differences in work styles, clothes and ornamentations between these two countries.

We have added the description in Discussion section (Page 16, first paragraph, lines 1--5).

**Reviewer 3:**
1. [K1] New Title is good!!

**R:** Thank you.

2. [K2] Overall “TEXT of this new rewritten ABSTRACT is fine.

**TO EDITOR:** Please help the author editing “ENGLISH” on some sentences.

**R:** We have made minor changes to polish the English with the help of colleagues with more experience in using English. Further more, we have reorganized and slightly shorten the ABSTRACT.
3. [K3] “,” not , There are many typos in the revised-MS, please double check before final submission.
**R:** We are sorry for this. In the current version of revised manuscript, we have done our best to correct these problems.

4. [K4] add
**R:** Done as suggested.

5. [K5] Rather use “its peak”. One peak & two peaks in this MS sounded strange to me!
**R:** We agree to reviewer’s comment. We changed the statement “The infection season typically spans March to November with one peak in summer usually between June to August” to “Because human infections typically occur between March and November with a peak occurrence in the summer between June and August, so the scrub typhus is also called “summer type” scrub typhus, which is transmitted by the Leptotrombidium deliense mite” (Page 6, 2nd paragraph, lines 3--6).

6. [K6] Please cited reference
**R:** Done as suggested.

7. [K7] Correction
**R:** Done as suggested.

8. [K8] This meteorological data might not be necessary
**R:** We have deleted the meteorological data according to the reviewer’s suggestion.

9. [K9] This was not study design and what cases meant?. Suggesting new title, such as “CRITERIA TO SELECT CASE STUDY”
**R:** Done as suggested.

10. [K10] patients
**R:** Done as suggested.

11. [K11] “suspected” would be better word!!!
**R:** We have changed the term “possible” to “suspected” in the revised manuscript. The same change has been made in other places of the manuscript where the same term was used.

12. [K12] Rewrite as followed: …. Past activities and information prior to his/her illness of enrolled patients were recorded. …
**R:** We have rewritten the sentence according to the reviewer’s suggestion (Page 9, first paragraph, lines 1--2).
13. [K13] suspected
   R: Done as suggested.

14. [K14] designed
   R: Done as suggested.

15. [K15] Correction
   R: Done as suggested.

16. [K16] Correction, because, all the lab-tests you did were dealing only on blood sample
   R: Done as suggested. We have changed the term “routine laboratory findings” to “routine hematological examinations” in the revised manuscript. The same change has been made in other places of the manuscript where the same term was used.

17. [K17] Add
   R: Done as suggested.

18. [K18] suspected
   R: Done as suggested.

19. [K19] Based on results from IFA examination
   R: Done as suggested.

20. [K20] Delete
   R: Done as suggested.

21. [K21] Correction
   R: Done as suggested.

22. [K22] Add
   R: Done as suggested.

23. [K23] What “The cases” meant? … Scrub typhus cases occurred ….
   These 3 sentences can combined. Please rewrite
   R: Done as suggested. We have reorganized the 3 sentences in the revised manuscript.

24. [K24] Delete
   R: Done as suggested.

25. [K25] one peak of what?
   R: We have changed the statement “During the study period, no case was found outside the September-December window. There was only one peak occurred in October during a year” to “During the study period, no case was reported before
September and after December and peaks of cases occurrences were all in October, followed by a sharp drop in case numbers” (Page 11, 3rd paragraph, line 3--4; Page 12, first paragraph, line 1).

26. [K26] Add
   **R:** Done as suggested.

27. [K27] Delete
   **R:** Done as suggested.

28. [K28] Rewrite:
   Of 480 confirmed cases, 56% (269/480) were male patients and 44% were female, respectively
   **R:** Done as suggested.

29. [K29] Delete
   **R:** Done as suggested.

30. [K30] Add
   **R:** Done as suggested.

31. [K31] Spelling
   **R:** Done as suggested.

32. [K32] Correction
   **R:** Done as suggested.

33. [K33-K34] [0] REWRITE as shown
   **R:** Done as suggested.

34. [K35] Suggest-change of title!
   **R:** Done as suggested. We have changed the title “Distribution of eschars sites” to “Location of eschars”.

35. [K36] REWRITE
   **R:** Done as suggested.

36. [K37-K41] Correction
   **R:** Done as suggested.

37. [K42] I would think there is a better way to explain these results, if you rewrite them in the different format++!!
   **R:** We have rewritten these results according to the reviewer’s suggestion (Page 14,
38. [K43] Can the authors use another terminology.
R: We use “peak occurrence” in the revision which we think it is appropriate to reflect the fact that frequency of case distribution over months. We have changed the sentence “In present study, seasonal variations in the autumn-winter type scrub typhus cases showed that the infection period was from September to December with a peak in October” to “In present study, seasonal variation pattern of the autumn-winter type scrub typhus cases showed that the infection period was from September to December with a single peak of case occurrence in October” (Page 14, 2nd paragraph, lines 1--3).

39. [K44] What areas the authors were compared to?
R: We compared the seasonal variation pattern of scrub typhus in northern China with those reported in Japan, and in southern China.

40. [K45] I bet there are better terminologies to be used
R: We agree to reviewer’s comment. We have changed the statement “In Japan, scrub typhus infection episodes with two peaks, one was in spring and another in October (the latter similar to the autumn-winter type) were found from 2000 to 2005” to “In Japan, a bimodal pattern of occurrence of cases – one in spring and another in October (the latter being similar to the autumn-winter type reported in current study) – was reported” (Page 14, 2nd paragraph, lines 7--9).

41. [K46] Delete
R: Done as suggested.

42. [K47] was this dates of September, if it was it should be written as September 11-20, year(s), or the authors would like to emphasized the period of the month, then it should written as “during the period of day 11-20 of September”
R: Done as suggested.

43. [K48] See K47
“during the period of day 11-20 of November”
R: Done as suggested.

44. [K49] I would rewrite this sentence. It’s too long
R: We have rewritten the sentence according to the reviewer’s suggestion (Page 15, first paragraph, lines 10--16).

45. [K50] Again, I would rewrite this sentence. It’s too long
R: We have rewritten the sentence according to the reviewer’s suggestion (Page 16, 2nd paragraph, lines 1--8).
46. [K51] This sentence does not belong here!
R: We have deleted the sentence in the revised version.

47. [K52] Why you put this statement here? If you would like to make your point that it was the same as your findings, this whole paragraph require to be rewriting.
R: We have deleted the statement “The mite has a predilection for attacking pressure points, such as boot tops and belt lines, and moist folds of skin” in the revised version.

48. [K53-K54] Either add “Year” of Cited Ref.#
R: Done as suggested.

49. [K55] IFA-test for serum sample; PCR was on blood samples, therefore, this sentence was incorrectly written!
R: We have changed the statement “Ten eschars from 10 cases whose blood samples were IFA-positive as well as PCR-positive were also tested positive by PCR (partial results have been published in reference 17)” to “Ten eschars from 10 cases whose serum samples were IFA-positive and blood samples were PCR-positive were also tested positive by PCR” (Page 18, 2\textsuperscript{nd} paragraph, lines 1--2).

50. [K56] This was to confirm that O. tsu were detected in all blood samples corrected from 10 patients with eschar, indicative that the patients were bitten by scrub typhus infected chiggers
R: We have added the reviewer’s discussion in the Discussion section in the revised manuscript (Page 18, 2\textsuperscript{nd} paragraph, lines 4--6).

51. [K57] Again the authors would like to express their limitation of the ELISA & IIP tests on this study, which was the weak-part of this study in term of confirmation of cases. IFA is OK if it was conducted by skill lab-person. However, it always provides false positive results. Therefore, the real-positives might be lower than expected. All those points I mentioned here should be discussed in the MS.
R: Thank you. The point raised by the reviewer was well appreciated. We have added the reviewer’s statement in the Discussion section in the revised manuscript (Page 18, 3\textsuperscript{rd} paragraph, lines 3--6).

52.[K58-K59] Correction
R: Done as suggested.

53. [K60] Suggestion to rewrite by stating your results with cited Ohashi’s findings
R: We have rewritten the paragraph according to the reviewer’s suggestion (Page 19, 2\textsuperscript{nd} paragraph, lines 1--20).