

March 25, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9014-cleared.doc).

Title: Seroprevalence and evolutionary dynamics of genotype 4 hepatitis E virus in Shandong Province, China

Author: Dong Yang, Mei Jiang, Zhi-Gang Qiu, Zhi-Qiang Shen, Wei-Hong Cui, Da-Ning Wang, Lian-Feng Gong, Bo Li, Xin-Wei Wang, Min Jin, Jun-Wen Li

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We have revised and modified the manuscript in accordance with the comments of editors and reviewers, and carefully proofread the manuscript to minimize typographical, grammatical, and bibliographical and format errors. Please find the revised manuscript with corrected sections marked in red for easier review purposes.

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer

(1) I am wondering why the authors did not sequence (at least in ORF2) by RT-nPCR the two serum samples which were positive for HEV RNA.

Answer: Thank you for your careful review and valuable suggestions. The 524 serum samples which were positive for HEV antibodies (IgG or IgM) were detected by RT-nPCR, and two of these infections were positive for HEV RNA. The

phylogenetic analysis showed that they all belonged to genotype 4 (Figure 1). Unfortunately, the genome sequences could not be determined due to exhaustion of the serum samples before completion of the full-length genome sequences.

(2) The discussion may be slightly shortened. The last paragraph of the discussion is not so relevant and should be re-written, emphasizing on the utility of phylogenetic analysis of HEV-4 strains circulating in China, in the South-East Asia region, and finally worldwide.

Answer: We have shortened the Discussion and rephrased the last paragraph of the Discussion as you suggested.

(3) Abstract: the conclusion “and this should be paid more attention” is too vague, general.

Answer: The sentence has been eliminated in the revised version.

(4) Introduction The topic is well presented. However, the last sentence for the aim of the study (including the “trans-regional” transmission) is somehow not so clear (if you don’t read the results section...). So, maybe it’s too early to define that in the introduction as an objective.

Answer: The last sentence in the aim of the study has been eliminated in the revised version.

(5) Results sections According to me, there’s a discrepancy between Tables 1 & 2. In Table 2, it was expected to obtain N° of positive IgG samples, $N=473+51=524$; in fact, it is written 509; also, when the authors are talking about IgM+ samples, are they also positive for IgG? Please clarify.

Answer: We are sorry for the misunderstanding due to unclear descriptions. There

were 524 serum samples which were positive for HEV antibodies (IgG or IgM). The results showed that 473 serum samples were only positive for IgG, and 51 individuals were positive for IgM which contained 36 IgG positive samples and 15 IgG negative samples. As a result, there were 509 (473+36) samples which were positive for IgG.

(6) Tables and Figures 1/ Table 2. Not so useful. 2/ Fig.3. It's necessary but it can be largely improved (more details and scale for people who does know China). 3/ Any additional figures for ORFs analysis? For TMRCA? 4/ I was not able to check Table S5 (as indicated in the last sentence of the first paragraph of the discussion). Please clarify.

Answer: We have improved the tables and figures following your suggestions:

- i. Table 2 presents the age-specific positivity of anti-HEV among the general population in Shandong Province, China in 2011. The anti-HEV results presented in Table 2 have been discussed in the text.
- ii. In Figure 3, the distance and scale have been added in the revised version.
- iii. ORFs analysis of HEV isolates in this study is shown in Supplementary Table S5, and the figure for TMRCA has been added (Supplementary Fig S2).
- iv. We are sorry for our negligence. The table mentioned in the last sentence of the first paragraph of the Discussion should be Supplementary Table S6, and correction has been made in the revised version.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Jun-Wen Li, MD, PhD

Department of Environment and Health

Tianjin Institute of Health and Environmental Medicine

No.1, Dali Road, Tianjin, 300050, China

Fax: +86-22-23328809

E-mail: junwen9999@hotmail.com