

Format for ANSWERING REVIEWERS

August 6, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 19905-Review.doc).

Title: Hepatitis E virus infection: Epidemiology and treatment implications

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Name of Journal: *World Journal of Virology*

ESPS Manuscript NO: 19905

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

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

Editor's and reviewers' comments

On a negative side I found that the layout of the tables is poor and should be improved:

1) Table 1: First column should be "countries", since authors classify them in "developing" (in development or low-medium income would be better designations) and "developed". Kashmir is a region but not a recognized country. United States is not properly spelled (an s is missing).

Response: As per suggestions, Table 1 has been modified.

2) Table 1: There are three columns dedicated to references. It would be better to place all information under the same column. For example, in the first line: "Mathur et al. (2001) [90]". I do not understand what numbers 35, 36, 30, etc... mean in the column

indicated as references. They are not reference numbers since those are indicated in brackets.

Response: All information is now under the same column to make it clear and easier to understand.

3) Table 1 would benefit from indicating information on prevalences of different genotypes in each case.

Response: We agree that such information would indeed be useful. Unfortunately, most of the cited studies merely provided HEV prevalence and did not include viral sequence analysis, which is normally required to definitively distinguish HEV genotypes.

4) Since references are included as columns in the table, it does not make sense to include them again in the table heading.

Response: We have eliminated such heading.

5) Table 2: A better title would be "Recent evidence on the outcome of therapies against acute hepatitis E infection", and again authors should not repeat references in the title and in the table contents.

Response: This has been changed.

6) "Type of article" should be "type of study"

Response: This has been changed.

7) The meaning of several abbreviations is missing: ALT4565, GFR, LFT (their meanings could be given in footnotes at the end of the table)

Response: These have been added.

8) Numbers and units should be separated: 1200 mg/day (not 1200mg/day).
Authors use “day” and “d” (please, use a single homogeneous designation)

Response: These have been addressed.

9) Most comments to Table 2 also apply to Tables 3 and 4 (title, study vs. article, abbreviations, etc...)

Response: Similar modifications were also made to these tables.

10) Kg should be used instead of kg (capital K required)

Response: The international standard for the “kilo” prefix is “k”. This also complies with the journal’s instruction to authors (Section “2.19 Units”).

11) In Table 4, the doses are missing in the first two examples.

Response: These patients were treated at the dosage of 135 µg/week and this information is now indicated.

12) Table 5: Column arrangement is poor. As presented, I suggest the following column designations: Year of study, Country, Technique used for detection, No of tests, Ratio of positive detections, References.

Response: Thank you for these suggestions. Column headings have now been changed.

13) Some logic in the order of countries is missing. If the first column is the “year of study”, then countries could be placed in alphabetical order and/or classified in geographic areas, for example.

Response: Studies are now listed by year, then by countries.

14) References should be written as in previous tables (journal should not be indicated). For example, “Bayfis et al. (2012) [xx]” (please, note that reference numbers are missing).

Response: These changes have been made.

15) A positive ratio of 0 is not correct in biology. A better option would be to write “none detected” or “ $<1/51,075$ ”

Response: This has been changed to “none detected”.

Additional comments:

1) P. 4, lines 6-7: “...encodes a protein of 114 amino acids associated...”

Response: This has been changed.

2) P. 5, lines 21-22: The sentence starting as “Furthermore, pathogen-free...” is not clear and should be rewritten.

Response: This sentence has been rephrased to say “pathogen-free pigs could be experimentally infected with human HEV genotypes 3 and 4”.

3) P. 6, lines 11-12: Authors state that acute HEV infection has higher mortality rates than HAV or HBV infections..., but they do not provide actual data (with appropriate references) for the last two infections. The sentence should be extended to provide this additional information.

Response: This sentence now reads “Acute HEV infection with pronounced symptoms resulted in higher mortality rates of 1-4% and up to 11%, compared to the mortality rates of acute HAV (1%) or HBV (1.5%) infection based on CDC Viral Hepatitis Surveillance data (2010).”

4) P. 6, lines 28-29: “...22 out of 38 individuals who tested positive...”

Response: This has been changed.

5) P. 6, line 30: “148 controls”. This sounds as jargon. What are the controls in those experiments? Authors should clarify their point.

Response: This sentence now reads “Compared to the control group of 148 individuals who had no markers for HEV infection, one independent factor associated with HEV infection was the consumption of game meat.”

6) P. 7, line 16: “...clearly understood [62]. However, a recent...”

Response: This has been changed.

7) P. 7, line 22: “has been reported”

Response: This has been changed.

8) P. 7, line 27: “synergistic”

Response: This has been changed.

Additional revisions according to editor's and reviewers' comments

1) Hepatitis E infection is a threat in countries where sanitation is poor. Of particular concern is the actual situation in Nepal after the recent earthquake. In 2014, this country suffered an outbreak with around 6,000 cases, and at least 9 deaths. Authors could perhaps include some comment on this issue and current threats and implications.

Response: We have added a paragraph in the discussion as follows: "Areas affected by natural disasters such as earthquakes and monsoon storms are also at risk of HEV epidemic. Displaced populations with limited access to clean drinking water, lack of sanitary facilities, overburdened health-care infrastructure, and immunologically naive population lacking protective antibodies combined will increase the likelihood of HEV transmission. Large outbreaks of HEV have occurred in Nepal, which in 2014 involved more than 10,000 cases."

1. Schematic representation of the virus structure

Response: Figure 1 now denotes the schematic diagram of the HEV genome.

2. A more detailed description of the pathogenetic mechanisms of the virus (ie cytopathic activity, role of the immune response in tissue damage.)

Response: We have added an additional section entitled "IMMUNE RESPONSES IN HEV INFECTION".

3. Provided more details about clinical manifestations and diagnostic criteria

Response: We have added additional details on the clinical manifestations and diagnostic criteria of HEV infection in “CLINICAL MANIFESTATIONS AND DIAGNOSTIC CRITERIA” part.

4.Incidence of HEV in blood donors from China and Thailand

Response: We have now included the incidence of HEV in blood donors from China in Table 5. However, there is currently no data on HEV among blood donors in Thailand.

5.Provide more details of the vaccine formulations and comment on their commercialization in various countries

Response: Additional details have been provided.

3 References and typesetting were corrected

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

Sincerely yours,

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