



Date: 17-11-2015

**Response to Reviewer Comments**  
**Hepatitis C virus prevalence and genotype distribution in Pakistan: A**  
**comprehensive review of recent data**  
**ESPS Manuscript ID 19050**

We are extremely grateful to worthy reviewers for their valuable comments and suggestions. The revised manuscript has been modified to address these concerns and suggestions as under:

**REVIEWER - 1**

The review “Hepatitis C virus prevalence and genotype distribution in Pakistan: A comprehensive review of recent data” reported by Umer M. and Iqbal M. is interesting and very useful for the scientific community. The study allows comprehensive information about the situation of HCV infection in a high prevalence area as Pakistan. However, the study has some limitations that must be resolved: (1)-In the tables summarizing the various HCV prevalence studies the authors should indicate not only the type of technique used but also the particular purchaser so that readers can assess the quality and performance of each study. In the same sense the text must add a comment on the possible presence of artifacts in these studies due to the technique used. (2)-There is no mention in any point of the manuscript or in the tables on methodologies used for genotyping and subtyping of patients, only a brief, but insufficient comment on the findings. It should be included in the results a comment on the methods used in different studies (LIPA sequencing? And the tables prevalence of genotypes / subtypes the particular technique used. Keep in mind that such techniques may alter significant prevalence data. (3)-Should be included in the discussion comments about preventive or therapeutic strategies for this population., and comments about the necessity of a reference methodology for HCV subtyping

Reply: The manufacturers of each method used in individual studies have been included in respective tables. Complete address of the manufacturer appears at the first instance of appearance and is not repeated in subsequent appearances. Likewise, a heading on page 15 (**COMPARISON OF METHODS USED IN SEROPREVALENCE STUDIES**) has been included to add a comment on comparative performance of techniques used in HCV diagnosis.

A comprehensive overview of genotyping methodologies used in cited studies has been added on page 17 under the heading **FREQUENCY DISTRIBUTION OF HCV GENOTYPES IN PAKISTAN** with subheading *Methodologies used for genotyping of HCV isolates*

The comment about preventive and therapeutic strategies has been added in conclusion (page 19/20). Discussion related to reference genotyping methodology has been added in related section (page 18).

## REVIEWER - 2

The manuscript by Umer M. and Iqbal M. reviewed the data regarding HCV prevalence in Pakistan. The review covered an important issue of HCV in Pakistan region. Pakistan has very high burden of disease and it is necessary to keep the knowledge update about its prevalence. The authors review the available information nicely and presented in an efficient manner. However I notice the missing of a recent article from Islamabad on HCV genotyping by Afzal et al. published in WJG 2014 Dec 14;20(46):17690-2. doi: 10.3748/wjg.v20.i46.17690. I recommend authors to search any other missing report. This article will be helpful for the readers and I recommend the publication of this article in WJG after minor revision. Minor revision: (1)- Inclusion of study by Afzal et al. published in WJG 2014 Dec 14;20(46):17690-2. doi: 10.3748/wjg.v20.i46.17690 and its discussion in context with untypable HCV genotypes prevalent in Pakistan. (2)- An extensive search of any other available report on the topic so the manuscript will include all available information.

Reply: Suggested reference and relevant discussion has been added (page 18 para 2). Likewise the relevant data has also been updated in text, table as well as figure 2.

At least two additional relevant publications were found, previously not included in this review. The studies (Afr Health Sci. 2014 Dec;14(4):810-5. and Biomedica 2013; 29: 70.) have been included in respective section (Patients seeking hospital care & Table 6: HCV seropositivity among patients other than liver disease, entry # 10 & 11).

## REVIEWER - 3

The authors reviewed recent 83 studies on HCV infection in Pakistan. The review is done in a good manner and the readers can acquire the appropriate information. I have only minor comments. Minor comments: Page 2, line 5. "84" should be "83", which is the actual number of studies which were reviewed. Page 11, HCV seroprevalence in blood donor. It should be mentioned whether HCV screening tests is routinely done in Pakistan.

Reply: On the suggestion of one of the worthy reviewers, three more studies were included (WJG 2014 Dec 14;20(46):17690-2; Afr Health Sci. 2014 Dec;14(4):810-5 and Biomedica 2013; 29: 70). So the number now has become 86 and the text now says 86 studies. However, the concern of reviewer has been addressed in essence as the number now represents the actual number of studies, which were reviewed.

Relevant information has been added in this section (page 11)

## REVIEWER - 4:

The authors made an interesting and exhaustive searching and analysis of HCV prevalence in Pakistan. This study is well discussed and contextualized in a general manner. However, the main question is the mathematical analysis to obtain the values of prevalence. I recommend present the formulas and the values of main variables used to calculate the weighted means. Other comments: Page 4, paragraph 2, flaviviridae must be capitalized. About the prevalence values in health care workers, are similar to the open or asymptomatic population?, please comment. The abbreviation IDUs (page 13, paragraph 2) was not previously presented. Although ICT, ELISA and other abbreviations are mentioned in the text, I suggest a brief list

below the Tables. CMIA is not previously mentioned. Figure 3, the colors of G1 and G3 are very similar and may be confused.

Reply: Formula for calculations has been given in cited reference. Nonetheless the same formula is now replicated in the text of this manuscript (page 8/9) as well.

Flaviviridae has been capitalized.

A comment has been added in the relevant section on prevalence values in HCV (page 14)

The abbreviation IDU has been defined at the first instance (Page 13)

List of abbreviations has been added in the manuscript

The color of G1 has been changed to avoid confusion.

**Note:** Page numbers mentioned by author in this reply refer to revised manuscript and might be different from the ones mentioned by worthy reviewers in their comments.

All of the aforementioned corrections, suggestions, comments etc, raised by all of the four learned Peer Reviewers, have been included in the revised manuscript, which is currently being uploaded. We hope that our revised manuscript will be accepted and get through to the publication stage of your esteemed journal.

Yours truly,

A handwritten signature in dark ink, appearing to read 'Mazhar Iqbal', with a stylized flourish at the end.

Mazhar Iqbal (PhD),  
Principal Scientist & Group Leader,  
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