**Author’s response to reviews**

**Title:** Exposure to hepatitis C virus in homeless men in Central Brazil: a cross-sectional study

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**Author’s response to reviews:**

Goiânia, 12-09-2016

Dear Editor,

We thank BMC Public Health for their thorough review. Each comment has been responded to in-line below.

The manuscript has also been subjected to a line review by a native English speaker with experience editing academic journal articles.

Reviewer #1:

Ferreira and colleagues investigated exposure to hepatitis C virus (HCV) in homeless men in Central Brazil using data from a cross sectional study. Manuscript generally well written and attempts to address an important public health issue among vulnerable populations. There are
strengths in this manuscript but I have concern about the use of age as a linear term in the bivariate and multiple regression models. Generally, I am in support of the manuscript. See more details below:

Abstract:

a) Error in line 20 at page 3 in the statement "of the following known risk factors for HCV infection were self-reported: …". Authors should re-write this statement for clarity and understanding.

Answer: The sentence was rewritten, as specified in the abstract (page 3):

Participants reported multiple risk behaviors, such as alcohol (78.9%), cocaine (37.1%) and/or crack use (53.1%), and inconsistent condom use (82.6%).

Background:

b) The authors provided sound and detailed background to the study. However, the authors should state clearly in the last paragraph the contribution(s) their study is expected to have on public health policies and interventions in the fight against HCV in homeless men. This is presently very minimal under this section.

Answer: Thank you reviewer for the sensitivity. We added some important information in the last paragraph of the background of the paper (page 4-5):

The approach to this infection requires different strategies both for diagnosis and for compliance with prevention and treatment protocols in the homeless. We believe that this study will contribute to the strengthening of public health and social policies aimed at the prevention of HCV in homeless person, since it presents important data about the epidemiological profile of the infection in this population in Brazil. In this way, the determinants of HCV exposure presented in this investigation can be taken into account in the planning and implementation of health promotion and infection prevention and comprehensive care actions, with emphasis on strengthening health education actions, availability of diagnostic tests in institutions that serve homeless persons, early treatment, provision of condoms, and epidemiological surveillance.

c) Error in line 18 at page 4. The statement "…behaviors, such injecting and…” should read "…behaviors, such as injecting and…".
The sentence was rewritten, as specified in the second paragraph of the background (page 4):

Therefore, individuals who practice specific risk behaviors, such as injection and non-injection drug use, sharing needles and syringes, unprotected sex, and multiple sexual partners, are at increased risk of HCV infection [4,6,7].

d) Error in line 29 at page 4. The statement "…men who have sex who men,…" should read "…men who have sex with men,…".

Answer: The sentence was rewritten, as specified in the second paragraph of the background (page 4):

In addition to behavioral determinants, factors related to social and programmatic vulnerabilities, such as low income and education, discrimination based on social condition or sexual orientation, loss of family ties, and difficulty accessing health services may contribute indirectly to the spread of HCV, especially in key populations (non-injection and injection drug users, sex workers, men who have sex with men, and homeless people) [8,9].

e) The statement "… ranging from 34.3% in Asia [15], to 19.0 to 26.5% in Europe…” in lines 45-47 at page 4 should be re-written for clarity and understanding. Also, the authors should be consistent in using the range of values for the percentages: why are some in ranges as in '4.84 to 66.0% in North America' while others are not as in 'ranging from 34.3% in Asia'?

Answer: Corrected. In addition, we added the variations based on our review of the literature, as specified in the fourth paragraph of the background (page 4):

Studies have shown a high prevalence of HCV among homeless men, ranging from 25.1 to 34.3% in Asia [15,16], 19.0 to 26.5% in Europe [9,17], and 4.84 to 66.0% in North America [18,19].

f) The statement "… the only study limited the Southeast region" in line 56 at page 4 should be re-written for clarity and understanding. It appears there is an omission.

Answer: The sentence was rewritten, as specified in the fifth paragraph of the background (page 4):
In Brazil, a country of continental dimensions, the extent of HCV infection among homeless men remains unknown, with the only study conducted about HCV epidemiology in this population being limited to the Southeastern region [11].

Methods:

g) The methods employed by the authors in the collection and analysis of the data appear sound to me. The methods employed were clearly described. However, the authors should briefly explain in one paragraph the need to use Poisson regression model with robust variance (e.g. clustered data or to take care of suspected misspecified model?) and its appropriateness. This will enable the readers understand and appreciate more the reason(s) for its use in this study.

Answer: We added the some justification to further clarify this to the reader in the statistical analysis sub session of methods (page 6):

“Studies indicate that in cross-sectional studies, Poisson models with robust variance are better alternatives than logistic regression. This modeling has been suggested as a good alternative to obtain estimates of adjusted prevalence ratios for potential confounding variables in epidemiological studies. In addition, the use of robust methods for estimating variance in Poisson models corrects the overestimation of variance, and produces adequate confidence intervals, especially when inserted into quantitative variable models”.

h) In addition, I am concerned about the use of age as a linear term in the final bivariate and multiple regression models. Studies have shown a non-linear effect of age on certain outcomes (dependent variables) so I suggest that the authors explore this because it can affect the final estimates from the models should non-linear effect of age be associated with HCV exposure.

Answer: Thank you for this insightful comment. Our outcome had a relatively low prevalence, partially undermining categorizations. To compare the two models, we performed two regression analyzes: one with the variable age continuous and another variable. We categorizes the variable according to a study conducted by Amiri et al. [2015 – reference list] among homeless person in Iran in 0. <40 years and> 40 years. Below, the two models specified in Table 2:
Table 2. Multiple regression analysis of risk factors associated with HCV exposure in homeless men in Central Brazil (age > 40 years)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Adjusteda PRb (95.0% CI)c</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt; 40 years)</td>
<td>3.41 (1.01-11.42)</td>
<td>0.046</td>
</tr>
<tr>
<td>Absence of family life</td>
<td>4.30 (1.12-14.38)</td>
<td>0.023</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>17.2 (5.28-58.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood transfusion history</td>
<td>0.71 (0.12-3.93)</td>
<td>0.680</td>
</tr>
<tr>
<td>Number of sexual partners</td>
<td>1.07 (1.04-1.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>STI history</td>
<td>3.15 (1.10-9.15)</td>
<td>0.037</td>
</tr>
<tr>
<td>R2: 0.356</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Multiple regression analysis of risk factors associated with HCV exposure in homeless men in Central Brazil (age continuous)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Adjusteda PRb (95.0% CI)c</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.07 (1.01-1.12)</td>
<td>0.008</td>
</tr>
<tr>
<td>Absence of family life</td>
<td>4.45 (1.39-14.3)</td>
<td>0.012</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>19.2 (6.01-61.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Blood transfusion history</td>
<td>0.91 (0.19-4.37)</td>
<td>0.913</td>
</tr>
<tr>
<td>Number of sexual partners</td>
<td>1.07 (1.04-1.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>STI history</td>
<td>3.34 (1.14-9.75)</td>
<td>0.027</td>
</tr>
<tr>
<td>R2: 0.367</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The 95.0% CI overlaps; R2 was slightly higher in the model with age as a continuous variable; In the analyses we used schooling, number of sexual partnerships, and length of time living on the street; Some studies have suggested the use of the continuous variable in the multiple regression model (For example: Royston 2006 [Dichotomizing continuous predictors in multiple regression: a bad Idea]. "Dichotomization of continuous data is unnecessary for statistical analysis and in
particular should not be applied”. In addition, we used a Poisson model with robust variance that controls potential overestimation of variances (Coutinho et al., 2008). We asked for permission to maintain our modeling using age as a continuous variable.

Results:

j) The statement "..., and duration of education eight years (IQR: 6-11)" in line 29 at page 6 should be re-written for clarity and understanding. It appears there is an omission.

Answer: The sentence was rewritten, as specified in the fifth paragraph of the results (page 7):

The median age was 36 years (IQR: 36-50), and schooling was eight years (IQR: 6-11).

Discussion and conclusion:

l) Authors could state clearly what their main contribution to the existing literature is to improve the message.

Answer: This was added in the first paragraph of the discussion (page 8):

This study investigated the HCV prevalence and risk factors among homeless men. To our knowledge, this is the first study conducted in homeless men in Central Brazil. The information in this study provides important data on the extent of HCV in this population, data that can guide actions to prevent and control infection by health services and social assistance to homeless persons. Our findings show a high prevalence of HCV infection in homeless men and an association with age, lack of family life, injection drug use, number of sexual partners, and STI history. In addition, the sample reported high rates of risk behaviors, suggesting that homeless represent a high risk group for pathogens transmitted by the parenteral route and/or sexually.

Tables:

m) The title for Table 1 at page 14 should read "… associated with HCV exposure in…” but not "… associated with exposure HCV in…”.

Answer: Corrected, as specified in the title of table 1 (page 15).

Table 1. Bivariate analysis of potential factors associated with HCV exposure in homeless men in Central Brazil
Reviewer #2:

I made comments on the article itself. The manuscript has many typos and grammars as well that the authors need to address. In conclusion, the manuscript is acceptable subject to minor corrections.

Abstract:

a) “…Cross-sectional study of 481 men…””Poisson regression with robust variance was…” of the following known risk factors for HCV infection were self-reported: …". Rewrite it.

Answer: Corrected, as specified in the methods of abstract (page 3):

…Methods: A Cross-sectional study was conducted in 481 men aged over 18 years attending therapeutic communities specialized in the recovery and reintegration of homeless people. Participants were tested for anti-HCV markers using rapid tests. Poisson regression analysis was used to verify the risk factors associated with exposure to HCV.

Background

b) “the only study limited the Southeast region”. Rewrite it.

Answer: The sentence was rewritten, as specified in the fifth paragraph of the background (page 4):

In Brazil, a country of continental dimensions, the extent of HCV infection among homeless men remains unknown, with the only study conducted about HCV epidemiology in this population being limited to the Southeastern region [11].

Methods.

c) Which studies?

Answer: We cited the studies used, as specified in the third paragraph of the session methods (page 5):

Data were collected through interviews using a structured questionnaire containing socio-demographic, behavioral, and clinical risk factors for HCV infection. The questionnaire was based on previously validated studies in populations of homeless and tested in a pilot study [11, 17-22].
d) What did you do for those who tested positive? WHO recommend that if the test is positive for anti-HCV antibodies, a nucleic acid test for HCV ribonucleic acid (RNA) is needed to confirm chronic infection because about 15–45% of people infected with HCV spontaneously clear the infection by a strong immune response without the need for treatment. Although no longer infected, they will still test positive for anti-HCV antibodies.

Answer: Dear Reviewer, Unfortunately due to budget issues, we could not perform the RNA test for positive cases. We recognize this limitation. It was added in the paragraph of the limitations in the discussion session, as specified (page 9):

“This study used as a marker the presence of anti-HCV rapid test without confirmation active infection through detection of viral RNA, not differentiating between current or past infection. However, the sensitivity and specificity of the rapid test is high using blood, serum or plasma (98.4% of sensitivity and 99.7% of specificity), is a good marker for exposure in vulnerable groups [43].”

e) Is there any particular reason you used K-S test? There are other tests such as the Anderson-Darling test and the Cramer Von-Mises test, which are refinements of the K-S test. And are considered to be more powerful than the original K-S test.

Answer: In fact, Anderson-Darling test is more powerful than K-S test [Razali NM, Wah YB. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. Journal of Statistical Modeling and Analytics. 2011;2(1):21-33]. Let us consider rectification and analysis. Due to non-normality, we chose to present continuous variables as medians. The correction is specified in the sub-session of the statistical analysis of session methods (page 6):

Data were analyzed using the statistical program STATA, version 12.0. The Anderson-Darling test was used to verify the normality of quantitative variables [25].

f) Why do you have to use Fisher's exact test? your sample is large enough..

Answer: Sorry. This sentence has been withdrawn. We used bivariate regression to select the variables for the Poisson regression model. This has been fixed and updated in the manuscript, as specified in the sub-session of the statistical analysis of session methods (page 6):

Bivariate regression analysis was performed to verify the potential exposure factors associated to HCV. Variables with p < 0.10 were included in a Poisson regression model with robust variance and considered statistically significant with values of p < 0.05 [26].
Results

g) …association between exposure by HCV and age. Rewrite it.

Answer: Corrected, as specified in the fourth paragraph of the discussion (page 8):

This study found an association between age and HCV exposure, as shown in other studies conducted in vulnerable populations [21,22,29-31].

The authors