PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Risk factors for blood borne viral hepatitis in health care workers of Pakistan; a population based case control study</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Gorar, Zulfikar; Butt, Zahid; Aziz, Imrana</td>
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VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Mohammad Salim wazir</th>
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<tr>
<td></td>
<td>Associate Professor</td>
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<td></td>
<td>Department of Community Medicine</td>
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<tr>
<td></td>
<td>Ayub Medical College Abbottabad</td>
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<td>Pakistan</td>
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REVIEW RETURNED 25-Feb-2014

GENERAL COMMENTS

1. Sample Size Calculations does not conform to a population based case-control study. Further assumptions i.e. exposure rates in cases and relative precision need to be taken into account.
2. Sampling Technique should be spelled out properly owing to it being a population based study.
3. The authors claim that it is a matched case-control study but there are 81 cases and 83 controls - how is it possible? For a matched case-control study like this there should have been matched analysis.
4. Study results are given for Hepatitis B and C separately that adds to confusion. This needs clarification.

A very good study and important one in the context of the country that can be accepted for publication after changes as suggested are incorporated.

REVIEWER

Saeed Hamid
Aga Khan University
Karachi

REVIEW RETURNED 09-Mar-2014

- The reviewer completed the checklist but made no further comments.

REVIEWER

Mohammad Tahir Yousafzai
The Aga Khan University, Karachi, Pakistan

REVIEW RETURNED 15-Apr-2014
**GENERAL COMMENTS**

**Overall comments:** The authors aimed to identify risk factors for hepatitis B and C antibodies among healthcare workers at first level care facilities in Sindh Province of Pakistan. The study is important and the results might be of interest to the policy makers and researchers in Pakistan. However, the study is not novel and it lacks necessary epidemiological rigors to warrant the publication of this paper in the current shape. Following are the detail comments for possible improvement of this manuscript:

1. **Overall language:** There are substantial sentence structure and grammatical errors. Therefore, the paper needs revision by an English language expert.
2. **Abstract:** There is a subtitle of intervention which describes the recruitment of subjects (cases and controls). The study is observational and hence no intervention is involved. Ideally, this subtitle should be removed.
3. **Introduction:** There are some abbreviations used which need to be spell out for the first time. Overall, there is no coherence in the introduction. No systematic flow of ideas and literature review is insufficient. Also, the authors have not identified any data gaps in the existing literature so that to provide a strong rationale for the conduct of this study. Last paragraph of introduction seems like methods section. No objective is reported at the end of introduction.
4. **Material and Methods:**
   a. **Case definition:** The authors have defined their case based on the presence of serum antibodies against hepatitis B or C virus. While the presence of hepatitis C antibodies shows infection, the other one is mostly done for checking the immunity against hepatitis B virus among healthy immunized population. The case definition seems to be inappropriate and might have resulted in powerful selection bias unless the authors justify or clarify this confusion.
   b. **Missing details:** The authors have not provided any details about sampling technique, recruitment process, data collection and laboratory methods/blood collection
etc. All these details need to be sufficiently provided under appropriate sub headings.

c. Statistical analysis: The authors have reported that logistic regression and multivariable logistic regression was done to identify the risk factors for hepatitis B and C. Since the design of this study was a matched case control, therefore the analysis is biased. Ideally, conditional logistic regression should be the appropriate analysis in match case control design.

d. Discussion: Some recently published papers from first level care facilities of Pakistan might be of interest to the authors in terms of comparing their results.


e. Conclusion: The conclusion is overly long and vague. Also, there are citations given in the conclusion which is not acceptable. Conclusion should be very concise and in line with main result and objective of the study.

**REVIEWER**
Muhammad Ali
University Roma Tre, Rome, Italy

**REVIEW RETURNED**
27-Apr-2014

**GENERAL COMMENTS**
In the present study, authors has described the prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection in healthcare workers in the Sindh Province of Pakistan. A high proportion of 11.7% and 24% of the healthcare workers were detected with active antibodies against HCV and HBV, respectively. The article also discusses the significance of different risk factors associated with the high prevalence of HCV and HBV in the studied population. I will highly recommend it for publication in BMJ Open; as the information provided in the article could be of value to the research community.
The following minor revisions are suggested:
1: The article reports that more than 10 years of education could be associated with the high prevalence of HCV and HBV in health care workers (line 36-40 at page 6 of the article). However, contrasting results have been reported at page 14-21 of page #7. These statements need revision.
2: The discussion on sero positive HBV healthcare workers needs further elaboration. In the line 27-32 page no. 7; it has been described that Anti-HBsAg remains active for 10 years in the vaccinated persons. The 20% of the HCW that are previously immunized against HBV could be due to the vaccination.
3: The statement: “Majority of female HCWs are lady health workers involved in immunization and were given inadequate training for injection delivery”, needs revision.

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<th>Reviewer 1: Name</th>
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<th>Point by point response</th>
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<tr>
<td>Sample Size Calculations does not conform to a population based case-control study.</td>
<td>A population-based case-control study is based on a well-defined source population from which all cases that arise in a given time period can be enumerated. Controls consist of random samples of persons without the disease of interest from the source population. Cases consist of all cases or a random sample of those cases(^1).</td>
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| | Formula used is  
\[
\left\{\frac{\sqrt{\left(\pi_1 (1-\pi_1) + \pi_2 (1-\pi_2) + \sqrt{2} \cdot \overline{\pi} (1-\overline{\pi})\right)}}{(\pi_2 - \pi_1)^2}
\right\}^2
\]  
Where  
\[
\pi_1 = \text{Proportion of control exposed} \\
\text{OR} = \text{Odds ratio} \\
\pi_2 = \text{Proportion of cases exposed, calculated from} \\
\pi_2 = \frac{\pi_1 \cdot \text{OR}}{1+ \pi_1 (\text{OR}-1)} \\
\overline{\pi} = \frac{\pi_1 + \pi_2}{2}
\]  
Further assumptions i.e. exposure rates in cases and relative precision need to be taken into account. | Needle stick injury (NSI) was taken as exposure, based on literature review of NSI in Pakistan; an exposure rate of 40% was assumed for controls. Relative precision is in built in the formula above which is taken from Essentials of Medical Statistics\(^1\). |

\(^1\) Gail MH, Case Control Study Population Based, Encyclopedia of Biostatistics,
Sampling Technique should be spelled out properly owing to it being a population based study

657 health care workers of district were screened against hepatitis and 227 were reported as reactive. Reactive subjects were taken as cases and non-reactive cases were taken as controls. Sampling of cases and controls was done by simple random sampling out of the database of 227. For every case a control was randomly selected from the same hospital.

The authors claim that it is a matched case-control study but there are 81 cases and 83 controls - how is it possible? For a matched case-control study like this there should have been matched analysis.

Study results are given for Hepatitis B and C separately that adds to confusion. This needs clarification.

Although routes of blood transmission are shared by the 2 viruses the risk of transmission for a similar exposure is disproportionally greater for the VHB than the VHC (10 fold and even greater). Pooling HCV and HBV infection is therefore not epidemiologically appropriate.

Reviewer: Mohammad Tahir Yousafzai

Overall comments: The authors aimed to identify risk factors for hepatitis B and C antibodies among healthcare workers at first level care facilities in Sindh Province of Pakistan. The study is important and the results might be of interest to the policy makers and researchers in Pakistan. However, the study is not novel and it lacks necessary epidemiological rigors to warrant the publication of this paper in the current shape. Following are the detail comments for possible improvement of this manuscript.

Overall language: There are substantial sentence structure and grammatical errors. Therefore, the paper needs revision by an English language expert.

Abstract: There is a subtitle of intervention which describes the recruitment of subjects (cases and controls). The study is observational and hence no intervention is involved. Ideally, this subtitle should be removed.

Subtitle intervention is deleted from Abstract

Introduction: There are some abbreviations used which need to be spell out for the first time. Overall, there is no coherence in the introduction.

1. Objective is added in the introduction.
2. Literature review on the risk factors of hepatitis in health care workers of Pakistan is almost non-existent hence
systematic flow of ideas and literature review is insufficient. Also, the authors have not identified any data gaps in the existing literature so that to provide a strong rationale for the conduct of this study. Last paragraph of introduction seems like methods section. No objective is reported at the end of introduction.

Material and Methods:

**Case definition:** The authors have defined their case based on the presence of serum antibodies against hepatitis B or C virus. While the presence of hepatitis C antibodies shows infection, the other one is mostly done for checking the immunity against hepatitis B virus among healthy immunized population. The case definition seems to be inappropriate and might have resulted in powerful selection bias unless the authors justify or clarify this confusion.

**Missing details:** The authors have not provided any details about sampling technique, recruitment process, data collection and laboratory methods/blood collection etc. All these details need to be sufficiently provided under appropriate subheadings.

**Statistical analysis:** The authors have reported that logistic regression and multivariable logistic regression was done to identify the risk factors for hepatitis B and C. Since the design of this study was a matched case control, therefore the analysis is biased. Ideally, conditional logistic regression should be the appropriate analysis in match case control design.

Discussion: Some recently published papers from first level care facilities of Pakistan might be of interest to the authors in terms of comparing their results.

1. Case definition is corrected to Hepatitis C antibody and Hepatitis B surface antigen.
2. Missing details on sampling technique of present study and recruitment process has been added under subtitle Sampling technique of Materials and Methods. Since laboratory procedure was not part of present study, details were skipped. However now the details are provided in the introduction. It is done so because present study is a follow up of an earlier lab based screening which is not part of this study.
3. We are not referring to our design as matched case control hence binary logistic regression is used.

Conclusion: The conclusion is overly long and vague. Also, there are citations given in the conclusion which is not acceptable. Conclusion
should be very concise and in line with main result and objective of the study.

Reviewer: 4 Muhammad Ali

The article report that more than 10 years of education could be associated with the high prevalence of HCV and HBV in health care workers (line 36-40 at page 6 of the article). However contrasting results has been reported at page 14-21 of page #7. These statements need revision.

Following sentence has been added in results section;
"Univariate analysis shows protective effects against both infections when formal education is 10 years or more, however in the multivariate model, it is a significant predictor for hepatitis C only (OR = 0.25, C.I$_{95}$ = 0.07 – 0.8)."

The discussion on sero positive HBV healthcare workers needs further elaboration. In the line 27-32 page no. 7; it has been described that Anti-HBsAg remains active for 10 years in the vaccinated persons. The 20% of the HCW that are previously immunized against HBV could be due to the vaccination.

Following elaboration is made;
"A small subset of 20% HCWs who were vaccinated against hepatitis B vaccine were also sero positive for hepatitis B. Hepatitis B vaccine confers an immunity level > 10mIU/ml of anti HBs Ag antibodies for at least 10 years, hence this inconsistent finding can be due to exposure of this group to hepatitis B virus prior to vaccination"

The statement: "Majority of female HCWs are lady health workers involved in immunization and were given inadequate training for injection delivery", needs revision.

Sentence is re phrased as under;
Low emphasis on safe injection practices during in service trainings can be a contributing factor which is reported to be erratic, unplanned and heavily dependent on donor funding.

VERSION 2 – REVIEW

REVIEWER: Mohammad Salim Wazir
Associate Professor
Ayub Medical College
Abbottabad
Pakistan

REVIEW RETURNED: 21-May-2014

GENERAL COMMENTS: The changes I had suggested have been incorporated.

REVIEWER: Mohammad Tahir Yousafzai
The Aga Khan University, Pakistan

REVIEW RETURNED: 22-May-2014
Overall comments: The authors have improved the manuscript however most of the comments and queries raised in the previous review are still not answered. Also, the authors have not provided annotated reply to each comment/query so that to understand the reason behind not incorporating the suggested changes. The authors are advised to provide point by point reply to each comment and in case they disagree with any comment they should justify their point. The paper needs major revisions for possible publication. Following are the detail comments for improvement:

1. Introduction:
   a. There are some abbreviations used (HCV, HBV, HIV) which need to be spell out for the first time.
   b. Page 3, second last para; Lines 39-49 “a HCW was defined … J&J USA Kits”, this para relate to methods and cannot be reported in the introduction section.
   c. Page 4, second para; Line#12-13, the authors provided the prevalence of antibodies for both hepatitis B and C virus in Jamshoro. This seems confusing because the presence of antibodies for hepatitis HBsAg are not considered as infection. How do the authors justify this? How can a person with full Hepatitis B immunization and higher antibodies titer against HBsAg be separated from a person with active infection? These queries need to be answered as the case definition of authors is also based on antibodies against HBV and HCV and without clarification one can argue against the selection criteria.
   d. Objective of the study should be reported at the end of the introduction

2. Material and Methods:
   a. Case definition (contradictory statements regarding the outcome): The authors have defined their case based on the presence of serum antibodies against hepatitis B or C virus. While the presence of hepatitis C antibodies shows infection, the other one is mostly done for checking the immunity against hepatitis B virus among healthy immunized population. The case definition seems to be inappropriate and might have resulted in powerful selection bias unless the authors justify or clarify this confusion. Several contradictory statements are given regarding the outcome definition. On page 5, para 1 under material and methods; line 27 “Reactive antibody titer to hepatitis B and C was taken as outcome” and lines 30-31 “cases were … presence hepatitis B surface antigen”. I strongly recommend to provide a uniform standard definition which is acceptable and correct all contradictory statements existent in the whole manuscript (including abstract).
   b. Page 5, para 1; line#8 “Data was entered into … for analysis” this sentence belong to statistical analysis and needs to be placed under statistical analysis section.
   c. Sampling technique: This section should be relocated above sample size calculation.
   d. Statistical analysis: This was a matched case control design (every case was matched with control based on workplace and cadre). The analysis done by the authors was logistic regression. For matched case control studies, conditional logistic regression should be done. Odds Ratios based on logistic regression are invalid for the matched design. I suggest the authors to redo the analysis and report ORs based on conditional LR model.

3. Results: Page 6, para 1; lines 7-12 “Although routes of … epidemiologically appropriate”. These sentences are not the part of result section and needs to be relocated to methods section (under sub-section statistical analysis).
**GENERAL COMMENTS**

Authors of the present study have described the prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection in healthcare workers in the Sindh Province of Pakistan. A high proportion of 11.7% and 24% of the healthcare workers were detected with active antibodies against HCV and HBV, respectively. The article also discusses the significance of different risk factors associated with the high prevalence of HCV and HBV in the studied population. I will highly recommend it for publication in BMJ Open.

| REVIEWER | Muhammad Ali  
University Roma Tre |
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<td>REVIEW RETURNED</td>
<td>23-May-2014</td>
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**VERSION 2 – AUTHOR RESPONSE**

<table>
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<tr>
<th>Reviewer 1: Name</th>
<th>Mohammad Salim Wazir</th>
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<td>4. Overall, there is no coherence in the introduction. No systematic flow of ideas and literature review is insufficient. Also, the authors have not identified any data gaps in the existing literature so that to provide a strong rationale for the conduct of this study. Last paragraph of introduction seems like methods section. No objective is reported at the end of introduction.</td>
</tr>
<tr>
<td>1. Abbreviations are spelled out now.</td>
</tr>
<tr>
<td>2. Our study is a follow-up of a province wide screening done in 2007. These lines describe the methodology of screening exercise undertaken in 2007. Laboratory procedures were not part of current study. Hence this comment may be deleted.</td>
</tr>
<tr>
<td>3. The current draft states “antibodies against Hepatitis C” and “presence hepatitis B surface antigen”. HBsAg is a sero marker of acute/chronic infection (reference # 12). In the first draft of manuscript a typographical error was made and antibodies against Hepatitis B were written.</td>
</tr>
<tr>
<td>4. Literature review on the risk factors of hepatitis in health care workers of Pakistan is almost non-existent hence only prevalence studies are cited.</td>
</tr>
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</table>
### Material and Methods:

1. **Case definition**: (contradictory statements regarding the outcome). The authors have defined their case based on the presence of serum antibodies against hepatitis B or C virus. While the presence of hepatitis C antibodies shows infection, the other one is mostly done for checking the immunity against hepatitis B virus among healthy immunized population. The case definition seems to be inappropriate and might have resulted in powerful selection bias unless the authors justify or clarify this confusion. Several contradictory statements are given regarding the outcome definition. On page 5, para 1 under material and methods; line 27 “Reactive antibody titer to hepatitis B and C was taken as outcome” and lines 30-31 “cases were …presence hepatitis B surface antigen”. I strongly recommend providing a uniform standard definition which is acceptable and correct all contradictory statements existent in the whole manuscript (including abstract).

2. **Statistical Analysis**: Page 5, para 1; line#8 “Data was entered into …for analysis” this sentence belong to statistical analysis and needs to be placed under statistical analysis section.

3. The authors have reported that logistic regression and multivariable logistic regression was done to identify the risk factors for hepatitis B and C. Since the design of this study was a matched case control, therefore the analysis is biased. Ideally, conditional logistic regression should be the appropriate analysis in match case control design.

4. **Results**: Page 6, para 1; lines 7-12 “Although routes of …epidemiologically appropriate”. These sentences are not the part of result section and needs to be relocated to methods section (under sub-section statistical analysis).

### Reviewer # 4: Muhammad Ali

**Institution and Country** University Roma Tre

**Response**

Authors of the present study has described the prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection in healthcare workers in the Sindh Province of Pakistan. A high proportion of 11.7% and 24% of the healthcare workers were detected with active antibodies against HCV and HBV, respectively. The article also discusses the significance of different risk factors associated with the high prevalence of HCV and HBV in the studied population. I will highly recommend it for publication in BMJ Open