PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	HCV seropositivity in inmates and in the general population: an averaging approach to establish priority prevention interventions
AUTHORS	Roux, Perrine; Sagaon-Teyssier, Luis; Lions, Caroline; Fugon, Lionel; Verger, Pierre; Carrieri, Maria Patrizia

VERSION 1 - REVIEW

REVIEWER	Milloy, M-J Faculty of Medicine, University of British Columbia, Canada; BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Canada
REVIEW RETURNED	10-Jun-2014

GENERAL COMMENTS	Exposure to hepatitis C virus (HCV) reaches near endemic levels in many studies of people who use injection drugs (PWID) and chronic infection can lead to serious liver-associated sequelae. Evidence is required to guide effective interventions to prevent viral transmission. As with HIV, exposure to correctional facilities is linked to higher rates of HCV seropositivity. However, the relative importance of specific in-prison risk behaviours, such as illicit drug use behaviours, tattooing and sharing personal hygiene items, is unknown. To shed light on these issues, the authors have prepared an analysis involving data from an HCV risk factor survey linked to antibody testing data among clients accessing a network of HIV/HCV clinics in both community and correctional settings in France. Using a propensity score matching approach, the authors attempt to control for the inherent selection bias introduced through non-random assignment to correctional or community settings. Using multivariable analysis, the authors rank the strength of the associations between various risk factors and HCV infection. This submission by Roux and colleagues addresses a matter of clear public health importance in France and many other global settings. The findings regarding elevated risk associated with illicit drug insufflation and tattooing among incarcerated individuals provide specific evidence to address the largely uncontrolled transmission of HCV among individuals who use illicit drugs and are involved in the criminal justice system. This study benefits from having a large number of observations, including a very large number of observations from individuals who are incarcerated. The analytical approach also has some strengths, especially the use of matching to address selection bias associated with incarceration. In light of these attributes, I suggest this manuscript demands serious consideration by the journal. However, I think the manuscript would benefit from some revisions and clarifications, detailed below; there

are a number of methodological concerns to be addressed as well.

1. According to the Results (p9), 65,892 individuals agreed to participate. How many declined to participate? Why does Table 1 include information on 65,892 individuals if complete questionnaire data was only available for 52,082 individuals?
2. It would be helpful if Table 2 contained HCV testing information; also, I would suggest that the authors should maintain a consistent format and number of decimal places for p-values in both Tables.
3. It is unclear to me if the authors accounted for the possibility that individuals contributed more than one test in the dataset. Is it possible that an individual was matched to themselves (i.e., once while incarcerated and once while in the community)?
4. It would be helpful if the authors could briefly discuss the infectious disease testing regimen in the correctional facilities — i.e., opt-in, opt-out, compulsory, nominal, etc. — and whether that could have systematically effected who was tested.
5. Research involving incarcerated individuals presents unique challenges, not least because individuals who are incarcerated may be unwilling to disclose illegal behaviours. It would strengthen the study if the authors could describe steps taken to address these issues including ways in which the privacy and confidentiality of prisoner reports were protected. Also, the authors should describe the study was reviewed by a research ethics board and whether informed consent was gathered for the participants.
6. Related to the point above, an issue of the study that the authors acknowledge is the use of lifetime behaviours and not behaviours that may have occurred recently or within correctional facilities. Do the authors have any other data which might illuminate patterns of risk behaviours within correctional facilities?
7. As I understand it, the regression analysis included all the incarcerated individuals with a match among the non-incarcerated clients, or 82% (4977 individuals) of the total. Did these individuals differ from the incarcerated individuals not included in the regression analyses?
8. Approximately three-quarters (77%) of non-incarcerated clients completed a questionnaire while almost all (98%) of incarcerated clients completed a questionnaire. In the authors' view, what explains this difference? Could this have introduced selection bias into the analyses?
9. The authors conclude that improved and expanded interventions to prevent the transmission of blood-borne pathogens are needed within local correctional facilities. The recognition that correctional facilities are the site of elevated levels of viral transmission is not novel; unfortunately, few jurisdictions have enacted meaningful reforms to curb the spread of infectious diseases within custodial settings. Perhaps the authors could discuss the barriers to the scale-up of harm reduction and other services within French correctional settings and comment on whether the nature of the French correctional health system is a help or hindrance to delivering evidence-based treatment and care to incarcerated individuals.
10. I am unfamiliar with the term "quasi-exhaustive" (page 16.) Perhaps a different term or some explanation would be better.
11. What is the "representative population" (page 13) sampled for this analysis? How do the authors know this sample is an unbiased reflection of that population?
12. The authors write that "serological HCV tests were systematically proposed to clients when at least one risk-factor [sic] was identified." (Page 5.) What were these risk factors? I presume that a lifetime history of incarceration was one of those factors. Does

	that mean that all incarcerated individuals were offered an HCV test, while only some of the non-incarcerated individuals were offered a test? In general, I suggest that the list of risk factors should be fully described. Thank you for the opportunity to review this manuscript.

REVIEWER	LIA POSSUELO UNIVERSIDADE DE SANTA CRUZ DO SUL, BRAZIL
REVIEW RETURNED	04-Jul-2014

GENERAL COMMENTS	minor revision - Add in the metodology ethics aspects. - To describe what test were done to identify HCV infection - Write what mean ELISA

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Reviewer Name Milloy, M-J Institution and Country Faculty of Medicine, University of British Columbia, Canada; BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Canada Please state any competing interests or state 'None declared': None declared.
Exposure to hepatitis C virus (HCV) reaches near endemic levels in many studies of people who use injection drugs (PWID) and chronic infection can lead to serious liver-associated sequelae. Evidence is required to guide effective interventions to prevent viral transmission. As with HIV, exposure to correctional facilities is linked to higher rates of HCV seropositivity. However, the relative importance of specific in-prison risk behaviours, such as illicit drug use behaviours, tattooing and sharing personal hygiene items, is unknown. To shed light on these issues, the authors have prepared an analysis involving data from an HCV risk factor survey linked to antibody testing data among clients accessing a network of HIV/HCV clinics in both community and correctional settings in France. Using a propensity score matching approach, the authors attempt to control for the inherent selection bias introduced through non-random assignment to correctional or community settings. Using multivariable analysis, the authors rank the strength of the associations between various risk factors and HCV infection.
This submission by Roux and colleagues addresses a matter of clear public health importance in France and many other global settings. The findings regarding elevated risk associated with illicit drug insufflation and tattooing among incarcerated individuals provide specific evidence to address the largely uncontrolled transmission of HCV among individuals who use illicit drugs and are involved in the criminal justice system. This study benefits from having a large number of observations, including a very large number of observations from individuals who are incarcerated. The analytical approach also has some strengths, especially the use of matching to address selection bias associated with incarceration. In light of these attributes, I suggest this manuscript demands serious consideration by the journal. However, I think the manuscript would benefit from some revisions and clarifications, detailed below; there are a number of methodological concerns to be addressed as well.
1. According to the Results (p9), 65,892 individuals agreed to participate. How many declined to participate? Why does Table 1 include information on 65,892 individuals if complete questionnaire data was only available for 52,082 individuals?
The reviewer is correct and we should have been clearer. A completed questionnaire means that all data including the results of HCV testing were available. We have now specified this in the results section:
"During the study period, 65892 screening tests were performed, and 53062 individuals agreed to participate. Among the latter, 980 had no medical data. Finally, our study group consisted of 52 082 (79%) participants who filled in a self-administrated questionnaire and had complete data from a

medical questionnaire: 46 125 (77%) in the general population and 5 957 (98%) in prison."
In addition, we decided to present the results in Table 1 among the 52 082 individuals, which seems to be more appropriate.
2. It would be helpful if Table 2 contained HCV testing information; also, I would suggest that the authors should maintain a consistent format and number of decimal places for p-values in both Tables.
We followed the reviewer's suggestions and added the % of positive HCV test in Table 2. We also kept the same format for all the p-values.
3. It is unclear to me if the authors accounted for the possibility that individuals contributed more than one test in the dataset. Is it possible that an individual was matched to themselves (i.e., once while incarcerated and once while in the community)?
To take into account the reviewer's comment, we added the following sentence in the limitations section of the discussion:
"Finally, as screening was anonymous, we are unable to say whether the same individual was tested more than once and so this could not be taken into account in the statistical analysis. The matching of the prison population and the general population, may have partially addressed such correlated events (e.g., the same person tested in prison and in the general population)."
4. It would be helpful if the authors could briefly discuss the infectious disease testing regimen in the correctional facilities — i.e., opt-in, opt-out, compulsory, nominal, etc. — and whether that could have systematically effected who was tested.
As suggested by the reviewer, we have better explained the testing regimen in the correctional setting in the following paragraph: "In prison, individuals willing to be tested for HIV or HCV had access to one of the 3 CDAG centres for HIV or HCV testing following the same protocol as that for the general population".
5. Research involving incarcerated individuals presents unique challenges, not least because individuals who are incarcerated may be unwilling to disclose illegal behaviours. It would strengthen the study if the authors could describe steps taken to address these issues including ways in which the privacy and confidentiality of prisoner reports were protected. Also, the authors should describe the study was reviewed by a research ethics board and whether informed consent was gathered for the participants.
The reviewer is correct and we added a paragraph to clarify the French context of HIV and HCV testing centers, which are very specific in terms of confidentiality and ethics. The paragraph reads as follows: "It is important to note that, in France, these "free and anonymous" centres for HIV and HCV testing are covered by confidentiality laws which protect individuals from being identified. All data recorded in this context are completely anonymous. Therefore anonymity was guaranteed for our study participants from both the general and prison populations".
For these reasons, the study did not need any research ethics board.
6. Related to the point above, an issue of the study that the authors acknowledge is the use of lifetime behaviours and not behaviours that may have occurred recently or within correctional facilities. Do the authors have any other data which might illuminate patterns of risk behaviours within correctional facilities?
This is a pertinent comment but we do not have further data regarding behaviours that may have occurred in prison. We appreciate that it is a study limitation. However we know that the correctional setting may exacerbate risky behaviors, especially in terms of drug use and HCV transmission. Accordingly, those who reported having more at-risk behaviors in their lifetime were probably more likely to have had more recent at-risk behaviors, especially in prison. We added this limitation to the discussion: "The use of lifetime at-risk practices and not recent at-risk practices or at-risk practices within correctional facilities may be a limitation. However, we know that the prison setting may exacerbate at-risk behaviours, especially in terms of drug use and HCV transmission. Accordingly, those who reported more at-risk behaviours in their lifetime were more likely to have had recent at-risk behaviours in prison."
7. As I understand it, the regression analysis included all the incarcerated individuals with a match

among the non-incarcerated clients, or 82% (4977 individuals) of the total. Did these individuals differ from the incarcerated individuals not included in the regression analyses?
The regression analysis implemented in this paper aimed to assess the differences between incarcerated and non-incarcerated people in terms of the risk factors associated with being HCV+. Carrying out regression analysis using the whole sample would have induced inaccurate inference given the important differences (sociodemographic and socioeconomic) between the incarcerated and non-incarcerated groups (Table 1). Indeed, these differences introduced a bias that could have compromised our results. For this reason it was necessary to deal with this "sampling bias" by carrying out our analysis under the case-control framework. In doing so, incarcerated individuals were defined as the "treated" group and non-incarcerated individuals were defined as the "control" group. The purpose of this technique is to construct identical groups (i.e. balanced groups) in terms of some characteristics: gender, age, education level etc. The propensity score technique provided 4977 matches (out of 6065 incarcerated participants) to non-incarcerated persons, resulting in a sample of 4977*2. The nature of the method implies that individuals not matched (1088 incarcerated and 54 850 non-incarcerated) are different to the analyzed group (treated-control matched individuals) in terms of the characteristics used for the matching method.
To take the reviewer's comments into account, we performed a comparison between incarcerated individuals included in the analysis and those incarcerated who were excluded from the analysis. We found that these two populations were different since those excluded from the analyses were less often employed, less educated, and more likely to be from an endemic native country. These results from the comparison suggest that those who did not find any counterpart in the general population were more likely to be a recent migrant.
8. Approximately three-quarters (77%) of non-incarcerated clients completed a questionnaire while almost all (98%) of incarcerated clients completed a questionnaire. In the authors' view, what explains this difference? Could this have introduced selection bias into the analyses?
This remark is interesting and should be discussed in the limitations section. One hypothesis is that incarcerated individuals had more time to fill in questionnaires, and accordingly we may have a more representative population in prison than in the community. We added a sentence in the limitations section to address this issue as follows: "It is interesting to note that almost all the incarcerated participants (98%) had both the completed self-administered and medical questionnaire, unlike only 77% in the general population. This may be due to the prison context where individuals have more time to fill in questionnaires".
9. The authors conclude that improved and expanded interventions to prevent the transmission of blood-borne pathogens are needed within local correctional facilities. The recognition that correctional facilities are the site of elevated levels of viral transmission is not novel; unfortunately, few jurisdictions have enacted meaningful reforms to curb the spread of infectious diseases within custodial settings. Perhaps the authors could discuss the barriers to the scale-up of harm reduction and other services within French correctional settings and comment on whether the nature of the French correctional health system is a help or hindrance to delivering evidence-based treatment and care to incarcerated individuals.
Following the reviewer's suggestion, we have improved the discussion of political and cultural contexts that impact access to effective harm reduction interventions in French prisons. We added this paragraph in the discussion section: "As in other countries, French prisons have not yet recognized the importance of accessing effective prevention strategies to reduce blood-borne infections transmission in correctional settings. This is because prevention initiatives regarding drug use are in prisons are implemented from a repressive perspective and not from a public health perspective [30]. However, our results showed the importance for decision makers to introduce more harm reduction interventions in prison, especially interventions targeting HCV transmission."
10. I am unfamiliar with the term "quasi-exhaustive" (page 16.) Perhaps a different term or some explanation would be better.
As suggested we removed this word and replaced it with an explanation: "First, this study encompasses almost all the centres for HIV and HCV testing for the PACA region (south-eastern

France). Furthermore, it is a regionally representative cross-sectional survey".
11. What is the "representative population" (page 13) sampled for this analysis? How do the authors know this sample is an unbiased reflection of that population?
The reviewer is correct and we have added: "representative population of those willing to be tested for HCV or HIV".
12. The authors write that "serological HCV tests were systematically proposed to clients when at least one risk-factor [sic] was identified." (Page 5.) What were these risk factors? I presume that a lifetime history of incarceration was one of those factors. Does that mean that all incarcerated individuals were offered an HCV test, while only some of the non-incarcerated individuals were offered a test? In general, I suggest that the list of risk factors should be fully described.
As suggested by the reviewer we added the list of risk factors: "…(injecting drug use, blood exposure, use of a sharp object with blood, etc.)."
Thank you for the opportunity to review this manuscript.
Reviewer: 2 Reviewer Name LIA POSSUELO Institution and Country UNIVERSIDADE DE SANTA CRUZ DO SUL, BRAZIL Please state any competing interests or state 'None declared': NONE DECLARED
minor revision
Add in the methodology ethics aspects.
As suggested by the reviewer, we added the following paragraph about ethics aspects in the methods: "It is important to note that, in France, these "free and anonymous" centres for HIV and HCV testing are covered by confidentiality laws which protect individuals from being identified. All data recorded in this context are completely anonymous. Therefore anonymity was guaranteed for our study participants from both the general and prison populations".
To describe what test were done to identify HCV infection.
We better described HCV diagnosis, as follows: "Every client with a positive Enzyme-Linked ImmunoSorbent Assay (ELISA) test for HCV was considered HCV positive. When a high level of transaminases was detected with the positive ELISA, a Polymerase Chain Reaction (PCR) was performed".
- Write what mean ELISA
We added the meaning of ELISA in the text: "Enzyme-Linked ImmunoSorbent Assay (ELISA)".

VERSION 2 – REVIEW

REVIEWER	Milloy, M-J Research scientist, BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Vancouver, BC, Canada Assistant professor, Division of AIDS, Department of Medicine, University of British Columbia
REVIEW RETURNED	31-Jul-2014

GENERAL COMMENTS	I thank the authors for their thoughtful and comprehensive responses to my comments on their original manuscript. I have no further concerns and recommend this submission be accepted for publication.