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| Title | Systematic review of the accuracy of antibody tests used to screen asymptomatic adults for hepatitis C infection |
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| **Reviewer 1** | Dr. Max Trubnikov MSc PhD MD |
| Institution | Public Health Agency of Canada, Centre for Communicable Diseases and Infection Control, Ottawa, Ont. |
| General comments (author response in bold) | 1. Introduction section, Page 3, line 33: I suggest re-wording "… but antibodies persist," into "… but antibodies may persist," to indicate the possibility of an alternative outcome (i.e. eventual reduction in antibodies titres resulting in the possibly undetectable levels of antibodies to HCV). Such a change may be supported by the following reference: Giuberti T, Ferrari C, Marchelli S, et al. Long-term follow-up of anti-hepatitis C virus antibodies in patients with acute nonA nonB hepatitis and different outcome of liver disease. Liver 1992; 12(2): 94-99.<br>**We have made the suggested edit and added the suggested reference.**<br><br>2. Introduction section, Page 3, line 38: I suggest adding anxiety as an example of potential harms.<br>**We have added 'anxiety' as an example of a potential harm.**<br><br>3. I suggest including PPV and NPV outcome measures somewhere in the text.<br>**PPV and NPV are included in our methods section as well as in our results Tables 3-4. Our GRADE table (Table 5) implicitly considers PPV and NPV when it provides the predicted values for true positives, false positives, true negatives, and false-negatives. To make the latter clearer, we modified the results section to state: "Findings from the remaining study (38) were assessed as 'very low' quality of evidence using GRADE (Table 5); this study reported a sensitivity of 81.8%, 95% CI (59.0-100%) and a specificity of 99.7%, 95% CI (99.6-99.8%). Assuming an HCV seroprevalence of 0.96% as in the general Canadian population (2), instead of the 0.1% prevalence among the 17,840 blood donors in the study (38), the PPV would be 72.7%, 95% CI (66.2-78.8%), and the NPV would be 99.8%, 95% CI (99.8-99.9%). Applying this study's findings to 1,000 individuals drawn from the general Canadian population (Table 5), we would expect 8, 95% CI (6-10) true-positives, 987, 95% CI (986-988) true-negatives, 3, 95% CI (2-4) false-positives, and 2, 95% CI (0-4) false-negatives."**<br><br>4. It is evident how the paucity and low quality of data has limited the choice of venues and the range of sensitivity/specificity estimates. Interpretation section may also include description of a potential limitation in the form of a selection bias that may have been introduced by the choice of blood donation centres as a suitable primary care venue (i.e. the study by Kosan et al, 2010). Unless Turkish Red Crescent donation policy suggest using remuneration or other incentives able to attract high-risk clients, blood donation centres would be dealing with a considerably healthier sub-population than other primary care centres, thus affecting the chosen outcomes of interest.<br>**Our limitations section states: "The applicability of our findings to the general Canadian population is limited because a majority of included studies were conducted among blood donors, and persons eligible to donate blood are at lower risk of blood-borne infections like HCV than the general population." However, it should be noted that only 2 of 7 studies involving blood donors had extremely low HCV prevalence (Kosan 2010 – 0.1% and Arora 2016 – 0.2%). Despite involving blood donors, 4 of 7 studies had a high (Ol 2009 – 2.3%) or extremely high (Tashkandy 2007 – 25.4%; Sommese 2014 – 69.2%; Rao 2009 – 21.2%) sample prevalence of HCV, which speaks to flaws in the study design, which are highlighted in the QUADAS-2 assessment. For 1 of 7 studies involving blood donors (Denoyel 2004), the sample prevalence could not be estimated. HCV prevalence for all included studies are reported in Tables 3 and 4.** |
| **Reviewer 2** | Dr. Sandra Steiner PhD |
| Institution | Centers for Disease Control and Prevention, Office of Public Health Preparedness and Response, Atlanta, GA |
| General comments (author response in bold) | 1. One typo found in Page 5, line 42 should read: "…as well as some of those…"<br>**We have made the suggested correction.**<br><br>2. In the Appendix Table 1. I suggest swapping the columns with the rows, so that more emphasis is placed on the tests used rather than on the Provinces and Territories.<br>**We have swapped the columns and the rows in Appendix A – Environmental Scan, Table 1.** |

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| | 3. The interpretation could be followed by suggested recommendations or interim guidance for clinicians to use when answering the question raised by the study. The recommendations should be based on the strength of the evidence and the results of the literature review. If the authors are planning a separate policy publication that will help guide clinicians and do not wish to address interim guidance and recommendations in this systematic review then they should state so as Future Studies/Research.<br>**We rewrote the last paragraph of the interpretation section to clarify this point. It now reads: "In conclusion, the availability of a 'safe, valid, and reliable' screening test is a primordial consideration for decision-making about screening (10-12), but our study has shown that further research is needed to adequately characterize the accuracy of antibody tests used to screen the general population for HCV infection. Our study focused on the accuracy of HCV screening tests; however, several other important factors must be considered when making decisions about HCV screening, including: the benefits and harms of screening, the benefits and harms of treatment for screen-detected cases, the cost-effectiveness of screening, as well as patient preferences related to screening. A review of the evidence related to these considerations is beyond the scope of the present study, but such a review is being performed by others in the context of the Canadian Task Force on Preventive Health Care's upcoming guidelines on HCV screening. To help inform decision-making about HCV screening, we encourage jurisdictions that have already adopted population-based (birth cohort) screening for HCV to carefully evaluate and report on the accuracy of antibody tests, as well as screening benefits and harms."** |