Dear Editor,

Thank you for the opportunity to resubmit our article 'Viral hepatitis in 2021: the challenges remaining and how we should tackle them'. Please accept our apologies with regards to the late resubmission of our article. This was due to IT issues in our NHS working environment and we have been working extremely hard to resubmit by the allocated deadline. We would be very grateful if you would still consider our resubmission.

Your comments have provided us with valuable and constructive feedback. We have included your suggestions about cost and availability of point of care testing, but felt that further detailed discussion regarding the diagnosis and management of HBV infections in low-middle income countries was beyond the scope of the review. This is explained in the main manuscript.

We have included a list of the reviewer's comments below to highlight how we have responded to each of these.

- Page 2: In the methods section, authors mention chronic kidney disease as a term used for searching. Should this include and/or liver disease?
  Chronic liver disease has been added to the search terms.
- Page 4: The authors categorically state that "Use of this vaccine in children has reduced the incidence of HAV infection by 80%". I think this should be amended to "reportedly reduced" as it was only found in 1 study.
  Thank you for highlighting this, we have amended this as advised.
- Page 4: Can the authors please elaborate on "who are likely to be exposed to HAV from their employment". What sort of employment?
  We have provided an example of construction workers who are exposed to raw sewage.
- Page 5: "people who inject drugs (PWIDs)", this acronym should be introduced on the previous page where "people who inject drugs" was first mentioned.
  The acronym has been introduced earlier as advised.
- Page 5: The MSM acronym was also introduced on the previous page and doesn't need to be mentioned again.

Thank you for highlighting this, this has been amended.

- Page 5: ?re-phrase "offering of vaccination" - line 121

  This has been amended to say "doing so has not entered widespread clinical practice."

- Page 9: ?Elaborate here on the issues in resource- poor settings

  We have highlighted that the issues are more challenging in resource poor settings but feel that further discussion is beyond the scope of this review.

  Page 9: Under defining cure – HBsAg, HBeAg, cccDNA etc is used here without an explanation or introduction, ie – surface antigen of HB **Thank you for highlighting this, the abbreviations have been explained as advised.**

- Page 10: Functional cure is first mentioned here but the definition is incomplete, ie it doesn't mention HBV DNA suppression off Rx etc. It is introduced again on page 12 but here it is misleading as functional cure is not "HBsAg loss in more than 30% of patients". This is inaccurate**.**

  Thank you for making these points. The definition of functional cure has been amended to include HBV suppression off treatment and the definition of functional cure on page 12 (now page 13) has been reworded.

  Page 11: POC testing is mentioned again but it should be specified that we need HBV viral load and/or HBeAg –status to inform decisions on maternal prophylaxis. These diagnostic assays are not readily available, costly etc **This has been changed to state that establishing HBeAg status can allow for empirical treatment with tenofovir in the third trimester. Thank you for your prompt regarding the cost and availability of diagnostic assays, we have included this as another remaining challenge in viral hepatitis.**

  Page 11: Instead of "seroconversion occurs below the age of 30 years and where a low or undetectable HBV-DNA level was maintained", suggest replacing "was" with "has been" to avoid the tense change **We have changed this as advised.**

  Page 13: Another categorical statement - "HBsAg loss after the development of advanced fibrosis does not negate the risk of development of HCC". Suggest

"while HBsAg loss minimises the risk, it does not negate…." **Thank you for this suggestion, this has been amended.**

- Page 14: Line 341 – "hepatitis B core-related antigen" – the acronym has already been introduced so this should be HBcrAg

  This has been amended.
- Page 15: For consistency, suggest putting (HDV) next to subheading.

  We have added HDV next to the subheading as advised.
- Page 15: Other studies suggest a higher prevalence of HDV. This should be acknowledged. See Rizzetto et al, The Changing context of hepatitis D. JHepatol. 2021 **Thank you for highlighting this and for your suggestion of a relevant reference. We have added that other studies suggest a higher prevalence and have listed additional references.**

  Page 16: ?mention that HDV RNA is needed to diagnose current infection. **Thank you, this has been added.**

  Disagree with the comment "novel approach". Testing of newly diagnosed HBsAg-pos patients for anti-HD should be adopted. **Thank you for this comment, this has been amended.**

  Page 17: Again for consistency put (HCV) after subheading **We have added HCV after the subheading as advised.**

  Page 18: SVR needs to be defined – ie sustained virologic response. **Thank you for highlighting this, this has been included.**
- Page 21: Line 504 – use "times" instead of "x"

  This has been amended.

  Page 21: Define BBV. **Thank you for highlighting this, this has been included.**
- End Page 22 to top 23: "treatment" is used 7 times in as nearly as many sentences **Thank you for highlighting this, these sentences have been re-worded as suggested.**

  Page 23: ? comment on the use of anti-HC testing in re-infections. **We have commented on the need to confirm re-infection with HCV RNA.**

  Page 25: introduce abbreviation for "HCV-positive", ie (HCV RNA+) **Thank you for highlighting this, this has been added.**

Page 26: For consistency add “virus” to Hepatitis E subheading and include (HEV) **This has been included.**

- Page 28: Define SOT

  This has already been defined in the previous paragraph.
- Page 29: ?comment on need to understand source of infections to guide public health decisions.

  This has been added to Table 2.
- Figure 2: ?comment on education/harm reduction

  Thank you for this suggestion, this has been included.

  Table 2: Under Hep B - ? after ” Identifying undiagnosed individuals “add linkage to care. **Thank you for this suggestion, this has been included.**

  Under Hep C - ? add “Harm reduction” under pub health priorities. **Thank you for this suggestion, this has been included.**

Thank you once again for the opportunity to write this article and for your ongoing support in making improvements.

Yours Faithfully,

Rebecca Dunn and co-authors