PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Systematic Review of the Global Epidemiology of Viral-Induced Acute Liver Failure
AUTHORS	Patterson, Jenna; Hussey, Hannah; Silal, Sheetal; Goddard, Liz; Setshedi, Mashiko; Spearman, Wendy; Hussey, Gregory; Kagina, Benjamin; Muloiwa, Rudzani

VERSION 1 - REVIEW

REVIEWER	Francesco Sera London School of Hygiene and Tropical Medicine
REVIEW RETURNED	27-Feb-2020

GENERAL COMMENTS	This paper present the results of a systematic review performed to summarised the evidence on global epidemiology of viral-induced acute liver failure. This review follow the protocol published in Patterson et al, BMJ Open, 2019. The paper is well structured and clear, the results are summarised in a clear way and the discussion is supported by the results. I reviewed the statistical aspects of this paper. The authors used appropriately standard random-effect models to summarise the prevalence or risk estimates. I share the author choice to not perform sub-group or meta-regression analysis given the paucity of the data. Given the low number of studies I think was a reasonable choice to give overall prevalence or risk estimates by pre-specified groups. As a minor points: a) perhaps in the strength and limitations box, the authors could state as first point what are the main results of their study, then report some limitations. b) I would use the terms "overall" or "combined" instead of "average" to described the pooled estimates. There are a small number of typos that I spotted during the revision: References: I think the protocol published in Patterson et al, BMJ Open, 2019 [Ref 10] is wrongly indexed in the text (e.g. line 69 page 3). Results: in line 151 the "average" estimate is 20% (95%CI=18; 35) instead of 19% (95%CI=7; 36) Supplementary figure 3: something went wrong in the forest plot for CMV and EBV

REVIEWER	Kate Bennett Surrey Clinical Trials Unit, School of Biosciences and Medicine, University of Surrey, UK
REVIEW RETURNED	13-Mar-2020

GENERAL COMMENTS	References need to be checked. For example the published protocol is referred to as reference 11, but is listed as reference 10. Where prevalence rates are compared between e.g. immunized countries vs non-immunized, or before and after introduction of immunization programme, it would be better to present the difference and its confidence interval, rather than separate prevalences and their respective confidence intervals, which then need to be compared by eye. If this approach is used, it is easy to see if the confidence interval (around the difference) contains 0. If it does not, then we would be confident that there is a difference (in the prevalence rates). I could only find one country (Argentina), which had before and after (introduction of immunization programme) values. Yet the authors state that "the prevalence of HAV induced ALF is markedly lower in countries with routine HAV immunization" suggesting that they have included other countries where this has occurred. The categorisation of I2 needs to be modified from I2 ≤ 40% to I2 ≤ 60% (for not important or moderate) and similarly so for 'considerable or substantial' (from I2 ≥ 40% to I2 ≥ 60%).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	
General comment: This paper present the results of a systematic review performed to summarised the evidence on global epidemiology of viral-induced acute liver failure. This review follow the protocol published in Patterson et al, BMJ Open, 2019. The paper is well structured and clear, the results are summarised in a clear way and the discussion is supported by the results. I reviewed the statistical aspects of this paper. The authors used appropriately standard random-effect models to summarise the prevalence or risk estimates. I share the author choice to not perform sub-group or meta-regression analysis given the paucity of the data. Given the low number of studies I think was a reasonable choice to give overall prevalence or risk estimates by pre-specified groups.	Response: Thank you for your thoughtful review and comments. We greatly appreciate the time you took to consider our manuscript.
Comment 1: Perhaps in the strength and limitations box, the authors could state as first	Response: The strengths and limitations box is formatted as per BMJ Open guidelines.

point what are the main results of their study, then report some limitations.	I can't find any guidelines on this box, but I would suggest that you partially agree with the review by starting with strengths rather than limitations unless the guidelines specifically ask you to start with limitations. So, " Thank you for the comment. We have rearranged the items in the box to start with the strengths of our study that reflect our major findings while maintaining the format as per BMJ Open guidelines" or something like that.
Comment 2: I would use the terms "overall" or "combined" instead of "average" to described the pooled estimates.	Response: We have changed all use of "average" to combined.
Comment 3: References: I think the protocol published in Patterson et al, BMJ Open, 2019 [Ref 10] is wrongly indexed in the text (e.g. line 69 page 3).	Response: References have been double-checked and this issue has been fixed.
Comment 4: Results: in line 151 the "average" estimate is 20% (95%CI=18; 35) instead of 19% (95%CI=7; 36)	Response: Thank you for pointing this error out. It has been corrected on page 6, lines 151-152.
Comment 5: Supplementary figure 3: something went wrong in the forest plot for CMV and EBV.	Response: This error has been corrected.
Reviewer 2	
Comment 1: References need to be checked. For example the published protocol is referred to as reference 11, but is listed as reference 10.	Response: References have been double-checked and this issue has been fixed.
Comment 2: Where prevalence rates are compared between e.g. immunized countries vs non-immunized, or before and after introduction of immunization programme, it would be better to present the difference and its confidence interval, rather than separate prevalences and their respective confidence intervals, which then need to be compared by eye. If this approach is used, it is easy to see if the confidence interval (around the difference) contains 0. If it does not, then we would be confident that there is a difference (in the prevalence rates).	Response: While we agree fully with the principle underlying this comment, we believe this would not be methodologically appropriate for this study as this would require us to first pool together studies that are too heterogeneously different in order to compare the prevalence rates of any two groups (largely not composed of the same countries).
Comment 3: I could only find one country (Argentina), which had before and after (introduction of immunization programme) values. Yet the authors state that "the prevalence of HAV induced ALF is markedly lower in countries with routine HAV immunization" suggesting that they have included other countries where this has occurred.	Response: Thank you for pointing this out. Our study only compares countries with routine HAV immunization at the time of data collection vs countries with no routine HAV immunization at the time of data collection. Having more countries with a before and after prevalence would have greatly strengthened the comparison. This has been noted in the limitations.

Comment 4: The categorisation of I2 needs to be modified from I2 ≤ 40% to I2 ≤ 60% (for not important or moderate) and similarly so for 'considerable or substantial' (from I2 ≥ 40% to I2 ≥ 60%).	Response: This change has been made on page 4, lines 107 & 108

VERSION 2 – REVIEW

REVIEWER	Kate Bennett Surrey Clinical Trials Unit, University of Surrey
REVIEW RETURNED	05-May-2020

GENERAL COMMENTS	Dear Authors, thank you for responding to previous comments. I only have one further comment regarding the text in the 'Data Synthesis and Analysis' section (page 4). The text currently reads Where "not important" or "moderate" heterogeneity existed between studies (I2≤40%) but this should be changed from 40% to 60% to include the moderate group. Similarly for the "considerable" or "substantial" this should be I2>60% (rather than 40%) Otherwise well done on getting this completed. It is important work.

VERSION 2 – AUTHOR RESPONSE

Comment	Response
Dear Authors, thank you for responding to previous comments. I only have one further comment regarding the text in the 'Data Synthesis and Analysis' section (page 4). The text currently reads Where "not important" or "moderate" heterogeneity existed between studies (I2≤40%) but this should be changed from 40% to 60% to include the moderate group. Similarly for the "considerable" or "substantial" this should be I2>60% (rather than 40%)	Thank you for pointing out this error. The text has been corrected to read on lines 107-110: Where “not important” or “moderate” heterogeneity existed between studies ($I^2 \leq 60\%$), pooled outcome measures were reported with 95% confidence intervals for each respective outcome. Where “considerable” or “substantial” heterogeneity exists between studies ($I^2 > 60\%$), forest plots and prevalence ranges calculated using the random-effects model were used to narratively describe each outcome.