PEER REVIEW HISTORY

ARTICLE DETAILS

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

VERSION 1 – REVIEW

REVIEWER	Giuseppe Biondi-Zoccai Sapienza University of Rome, Latina, Italy I have consulted for Abbott Vascular and Bayer.
REVIEW RETURNED	01-Apr-2019

GENERAL COMMENTS	The proposed review protocol is of high quality. I have however the following minor suggestions: 1. The search could be piloted to make sure it works as intended. 2. The inclusion strategy seems overly generous: "Published and unpublished case-series, cross-sectional, cohort and randomized control trials (RCT) and non-randomized control trials". Please provide more details on how you would like to pool effect estimates from such disparate study designs. 3. I recommend to add a meta-regression analysis on top of standard ones.

REVIEWER	Yoshiharu Fukuda Teikyo University
REVIEW RETURNED	02-Apr-2019

GENERAL COMMENTS	The protocol might be suitable. But I think the study should be published as not the protocol paper but full paper that includes results and discussion.

REVIEWER	Kate Bennett Comprehensive Clinical Trials Unit Institute of Clinical Trials and Methodology University College London United Kingdom
REVIEW RETURNED	10-Apr-2019

GENERAL COMMENTS	7. I am a statistician but am not an expert in meta analysis therefore cannot comment on the statistics as described here. However, I make the following comments: The subgroup analysis (p8) does not define the age categories to be used.

	The sensitivity analysis (p9) describes 3 ways of looking at the intervention effects estimates but does not give any indication of how inconsistencies (if there are any) will be dealt with. 13. The page numbers quoted in the PRISMA checklist don't seem to match the page numbers in the document I have; perhaps need to be checked. The search criteria described do not mention the registers (eg clinicaltrials.gov; EudraCT) as a possible source of eligible studies. Might be worth exploring. The one month window for authors to respond to requests for missing data seems quite short. Overall the protocol is very well presented, the study well thought through and the research questions the study aims to answer are important ones.

REVIEWER	Francesco Sera LSHTM UK
REVIEW RETURNED	11-Apr-2019

GENERAL COMMENTS	This paper present the protocol for a systematic review aiming to give an epidemiological overview of viral induced acute liver failure (ALF). The paper is well written and well structured. From my point of view, the main issue of this project is the lack of specificity of the aims. I think the research question is too wide to be addressed in a single project. Moreover, the literature does not seems support this ambitious project. The authors listed three primary and secondary objectives: 1) estimate the prevalence/incidence of ALF; 2) evaluate the natural history of viral-induced ALF; 3) calculate the attributable ALF cases to each viral aetiological cause. About the first objective, that is to estimate the prevalence/incidence of ALF. The main issue is the definition of the denominator on which incidence or prevalence are calculated. Nationwide studies looks difficult as they do require a surveillance or notification system. Looking at the literature (I used the search strategy given by the authors in table 1), more often the incidence (or risk) of ALF is calculated in cohort defined by subject affected by virus. A more specific and feasible aim would be to estimate the incidence, risk or prevalence on cohort of subjects with infection with different viruses listed by the authors. Note that “Types of participants” section (Page 6 lines 18-25) wrongly require that a subject should have ALF and infection with any of the virus listed by the authors, when, in fact to assess objective 1) the patients have to be infected by any of the virus listed by the authors. Objective (2), that is evaluate the natural history of viral-induced ALF could use the cohort on which the study population is defined by the ALF and concurrent infection with any of the virus listed by the authors. Looking at the literature it seems that the cohort studies tend to consider a specific virus, so, perhaps this analysis need to be stratified by the virus considered in each study. I cannot see how objective 3) could be addressed. This would require a case-control study or a comprehensive characterisation of a well defines ALF case series, that does not seems frequent in the literature.

	The “Data synthesis” section (page 9 lines 38-43) should contain more information on the methods to pool incidence, risk or prevalences. As this task require specific methods (e.g. Barendregt, Jan J., et al. "Meta-analysis of prevalence." J Epidemiol Community Health 67.11 (2013): 974-978). For example, which transformation are the authors planning to use (Log transformation, square root transformation, or Freeman-Tukey Double arcsine transformation)? Which method (Fixed effect, random effect or exact likelihood method) are planning to use? Given the lack of specificity of the research question, I’m expecting an high level of heterogeneity across different incidence, prevalence estimates. Probably, part of the heterogeneity would be due to the different viruses that characterised the different cohort studies. My suggestion is to perform subgroup analysis based on the virus used to define the different cohort studies.

VERSION 1 – AUTHOR RESPONSE

We have carefully considered the editorial and reviewer comments made and have responded to each comment in the attached document. Changes reflecting our response to these comments can be seen in our revised manuscript submitted.

The authors also provided a marked copy with additional response. Please contact the publisher for full details.

VERSION 2 – REVIEW

REVIEWER	Giuseppe Biondi-Zoccai Sapienza University of Rome, Latina, Italy I have consulted for Abbott Vascular and Bayer.
REVIEW RETURNED	21-May-2019

GENERAL COMMENTS	The manuscript has been satisfactorily addressed.

REVIEWER	Francesco Sera LSHTM UK
REVIEW RETURNED	13-Jun-2019

GENERAL COMMENTS	The authors have addressed most of the major points of my previous review. I still think that it's an ambitious project, but the aims are more clearly stated in this version of the manuscript. The "Data Synthesis" section is still a bit vague in my opinion. In this meta-analysis there are two main occurrences measures: prevalences and incidence/mortality rates. These measures have different statistical properties; e.g. prevalences can be modelled as determination of Binomial random variables, while incidence rates can be modelled as determination of Poisson processes. The authors should more clearly stated which method are planning to use for combining proportions and incidence rates. For example for proportion fixed effects and random effects model can be used after considering the arcsin transformation, for incidence rate specific methods (e.g. as implemented in the metarate function of the R package metaphor) can be used. In this context I think the

	Mantel-Haenszel (fixed not random effects) is not useful as it applies for combining Odds ratios.

VERSION 2 – AUTHOR RESPONSE

Reviewer Comment	Comment Response
The authors have addressed most of the major points of my previous review. I still think that it's an ambitious project, but the aims are more clearly stated in this version of the manuscript.	Thank you for this comment, we appreciate your review of our protocol.
The "Data Synthesis" section is still a bit vague in my opinion. In this meta-analysis there are two main occurrences measures: prevalences and incidence/mortality rates. These measures have different statistical properties; e.g. prevalences can be modelled as determination of Binomial random variables, while incidence rates can be modelled as determination of Poisson processes. The authors should more clearly stated which method are planning to use for combining proportions and incidence rates. For example for proportion fixed effects and random effects model can be used after considering the arcsin transformation, for incidence rate specific methods (e.g. as implemented in the metarate function of the R package metaphor) can be used. In this context I think the Mantel-Haenszel (fixed not random effects) is not useful as it applies for combining Odds ratios.	Thank you for pointing this out. We have made an amendment to the “Data Synthesis” section, which now reads on Page 8, Lines 261-265 as follows: “Prevalence data from individual studies will be pooled together using random-effects meta-analysis. The pooled estimates will be calculated after a Freeman-Tukey double arcsine transformation and presented in forest plots. For incidence data, meta-analysis models will be applied using the log incidence rates and the corresponding standard errors. The pooled data will be reverse transformed and presented in forest plots. For rare events, incidences will be pooled using Poisson based mixed-effects models.”

VERSION 3 – REVIEW

REVIEWER	Francesco Sera Lshtm Uk
REVIEW RETURNED	24-Jul-2019

GENERAL COMMENTS	I Think the authors adress adequately to the point I rose in my previous review.