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A Systematic Review of the Global Epidemiology of Viral-Induced Acute Liver Failure

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Keywords:	Epidemiology < INFECTIOUS DISEASES, acute liver failure, VIROLOGY

PROTOCOL

A Systematic Review of the Global Epidemiology of Viral-Induced Acute Liver Failure

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ABSTRACT

Objective: This systematic review aims to describe the global epidemiology of viral-induced acute liver failure.

Setting: The global burden of viral-induced acute liver failure is largely unknown even with mortality rates associated with the disease varying between 60% and 80%, depending on the disease aetiology as well as a patient's access to care.

Methods and analysis: Electronic databases will be searched for relevant literature published from 2009 up to 2019. Published and unpublished case-series, cross-sectional, cohort and randomised control trials (RCT) and non-randomised control trials (nRCT) will be eligible for inclusion in this review. Qualifying studies will be formally assessed for quality and risk of bias using a scoring tool. Following standardised data extraction, meta-analyses will be carried out using STATA. Depending on characteristics of included studies, subgroup analyses will be performed. This review will be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

Conclusions: Establishing the common aetiologies of viral-induced acute liver failure, which vary geographically, is important so that: a) treatment can be initiated quickly, b) contraindications to liver transplant can be identified, c) prognoses can be determined more accurately, and most importantly, d) vaccination against viral ALF aetiologies can be prioritized especially in under-resourced regions with public health risks associated with the relevant attributable diseases.

Ethics and dissemination:

Trial Register: This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42018110309.

Key words: global, epidemiology, acute liver failure

Strengths and limitations of study:

- Comprehensive and exhaustive search for relevant studies from several databases
- Comprehensive diagnostic inclusion criteria for acute liver failure cases according to international guidelines
- Paucity of data may lead to meta-analysis not being possible for all global regions
- Diversity of viruses attributable to ALF cases may lead to low statistical power in meta-analysis

MAIN TEXT

INTRODUCTION

Acute liver failure (ALF) refers to a rare syndrome characterized by an acute liver injury resulting in encephalopathy (altered mentation) and coagulopathy (International Normalized Ratio (INR) >1.5) in individuals without known pre-existing liver disease and with an illness of <26 weeks duration (1). The syndrome was originally defined as fulminant liver failure or fulminant hepatic failure in 1970 but was re-defined as ALF in the early 1990s when the understanding of the multiple disease aetiologies, frequency of complications and prognosis of the condition further developed (2). Further sub-classifications of ALF include hyperacute, acute and subacute depending on the time in weeks from the development of jaundice to the development of hepatic encephalopathy (3).

The pathogenesis of ALF includes both direct and immune-mediated liver injury triggered by the disease aetiology (4). The aetiology of ALF determines the clinical course and progression of the disease and well as the need for specific therapy (5). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver diseases (acute fatty liver of pregnancy, HELLP syndrome, preeclampsia), vascular causes (Budd-Chiari syndrome, ischaemic hepatitis) and malignancy (lymphoma, haemophagocytic lymphohistiocytosis). Wilsons disease, vertically-acquired hepatitis B and autoimmune hepatitis are included despite being chronic liver diseases if the diagnosis is made within 26 weeks (6).

Acute viral hepatitis (particularly acute hepatitis A and acute E) has been identified as the most common cause of ALF among all ages in Asia and Africa and the most common causes of ALF in children in Asia and South America (2, 4). The incidence of virally induced ALF has substantially declined in Europe, with only 19% of all ALF cases now related to viral infection (2). Vaccination has led to a significant drop in the incidence of acute hepatitis B induced ALF, with fewer than 4% of ALF cases now attributable to hepatitis B infection in Europe (2). Since the introduction of a universal one-dose hepatitis A vaccination program in Argentina, the number of acute hepatitis A induced ALF cases has decreased from 54.6% to 27.7% (7).

The most common causes of death in patients with ALF are cerebral oedema and multi-organ system failure (4). Mortality rates associated with ALF vary between 60% and 80%, depending on the disease aetiology as well as a patient's access to care (8, 9). Liver transplantation plays a central role in the management of ALF and remains the only definitive treatment for patients who fail to demonstrate spontaneous recovery (1). It remains difficult to predict which ALF patients will require transplantation and models such as the "Model for End-stage Liver Disease" (MELD) have not improved the accuracy of these predictions (1). The King's College Criteria for emergency liver transplantation remains the most clinically useful, with a sensitivity of 68%-69% and a specificity of 82%-92% (10). Management of ALF cases accounts for 5-12% of all liver transplant activity in the United States and Europe (11). A large proportion of ALF patients in both high and low resource settings, however, are deemed to have

contraindications to transplantation or deteriorate beyond transplantation before a donor liver is allocated (5, 11, 12).

The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence in general (2). Epidemiological estimates around ALF are based purely on data from transplant units and the medical management of the condition remains poorly defined (1, 2). Establishing the common aetiologies of viral-induced ALF, which vary geographically, is important so that: a) treatment can be initiated quickly, b) contraindications to liver transplant can be identified, c) prognoses can be determined more accurately, and most important, d) vaccination against viral ALF aetiologies can be prioritized especially in under-resourced regions with public health risks associated with the relevant attributable diseases.

To the best of our knowledge, no extensive systematic review of the global epidemiology of viral-induced ALF has previously been conducted. Furthermore, synthesized data on the relative contribution of different viruses to the aetiology of ALF is missing in the field. Hepatitis A, is a major cause of ALF and the epidemiology of the disease is changing on a global scale. For example, it has been reported in many low and middle-income countries, that the epidemiology hepatitis A is transitioning from high to intermediate endemicity and this transition is associated with an increasing incidence of acute hepatitis A (13-15). This review aims to describe the global epidemiology of viral-induced ALF.

Objectives

To describe the global epidemiology of viral-induced acute liver failure from 2005 up to 2019.

Primary objectives

- To estimate the burden (prevalence, incidence, hospitalization rates including access to intensive/high care units, transplantation rates, case fatality rates) of viral-induced ALF

Secondary objectives

- To estimate the number of viral-induced acute liver failure cases attributable to each viral aetiological cause of acute liver failure

METHODS

Patient and Public Involvement

This research question was developed as part of an ongoing project by the research team that aims to generate evidence to facilitate evidence-based decision making of introducing routine hepatitis A vaccination in South Africa. The findings of this review will contribute to the knowledge base that aims to enhance global vaccination strategies against viral-associated ALF. As this is a systematic review, no patient involvement will be required; however, it is hoped that the findings of this review will help to highlight the burden that acute liver failure places

on populations without routine hepatitis A vaccination. Findings will be disseminated through publication in a peer reviewed journal and included in a technical policy dossier distributed to the National Advisory Group on Immunisation in South Africa.

Criteria for considering studies for this review

Types of studies

Published and unpublished case-series, cross-sectional, cohort and randomized control trials (RCT) and non-randomized control trials (nRCT) will be eligible for inclusion in this review.

Types of participants

Patients of any age diagnosed with acute liver failure and concurrent infection with any of the following viruses: Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV), coxsackievirus (CA16) and adenovirus (HAdVs).

Case definition

Included studies must have a clearly stated case definition of viral-induced acute liver failure. Cases must be confirmed by both clinical and laboratory diagnostic methods.

- Clinical diagnosis of ALF will be defined as follows for children and adults presenting with an acute liver injury:
    - Children – The absence of known, chronic liver disease with liver-based coagulopathy not responsive to parenteral vitamin K and an international normalized ratio (INR) ≥ 1.5 in the presence of clinical evidence of encephalopathy or INR of ≥ 2.0 without clinical signs of encephalopathy (16)
    - Adults – Liver-based coagulopathy (INR ≥ 1.5) and any grade of hepatic encephalopathy (HE) as defined by the West Haven criteria within 26 weeks after the onset of symptoms but with no evidence of chronic liver disease, including cirrhosis (1, 17)
- Serological, molecular or culture laboratory confirmation of infection with HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 or HAdVs.

Exclusion criteria

Studies will be excluded from this review if they do not report any of the primary outcomes listed or do not match the clearly stated case definition of viral-induced acute liver failure given for this review.

Outcomes

Primary outcomes

- Point prevalence of viral-induced ALF
- Incidence of viral-induced ALF
- Hospitalization rates of viral-induced ALF
- Case fatality rates of viral- induced ALF
- Liver transplant rates of viral- induced ALF

Secondary outcomes

- Proportion of viral-induced ALF cases attributable to each aetiological cause of viral ALF

Search Methods

The literature search strategy will use both text words and medical subject heading (MeSH) terms. It will include the following terms: epidemiology, prevalence, incidence, burden, mortality, morbidity, fulminant hepatic failure, fulminant liver failure, acute hepatic failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV) and coxsackie virus. These terms will be adapted for use in each defined database and then will be combined with a relevant filter to select studies eligible for inclusion in the review. **Table 1** shows an example search strategy for use in PubMed.

The following electronic databases will be searched for relevant published literature: EBSCOhost, PubMed, ScienceDirect, Scopus, Web of Science, Ovid, CINAHL and EBM Reviews. Grey literature will be sourced by consulting with expert researchers in the field and by searching the following electronic databases: OpenUCT, OpenGrey, Mednar and CORE. Databases will be searched for literature from 2009 up to 2019. The starting date of 2005 was chosen as Bernal et al. 2010 completed searched Medline with the terms “acute liver failure” and “fulminant hepatic failure” between 1997 and 2009 and provided a review of the most relevant publications to practice. No language restriction will be places on the search for studies (8).

Table 1: Search strategy for use in PUBMED

Query	Fields	Search term
#1	All fields	epidemiology OR prevalence OR incidence OR burden OR mortality OR morbidity
#2	All fields	fulminant OR acute
#3	All fields	hepatic failure OR liver failure

#4	All fields	hepatitis a virus OR HAV OR hepatitis b virus OR HBV OR hepatitis c virus OR HCV OR HCV OR hepatitis d virus OR HDV OR hepatitis e virus OR HEV OR epstein-barr virus OR EBV OR herpes simplex virus-1 OR HSV1 OR herpes simplex virus-2 OR HSV2 OR varicella-zoster virus OR VZV OR parvovirus b19 OR human parainfluenza viruses OR yellow fever virus OR YFV OR human herpesvirus 6 OR HHV-6 OR cytomegalovirus OR CMV OR adenovirus OR HAdVs
#5	All fields	humans
#6	N/A	#1 AND #2 AND #3 AND #4 AND #5

Selection of studies

Two authors, JP and LA, will screen the search outputs by reading the titles and abstracts, guided by the inclusion and exclusion criteria. JP and LA will then independently screen the full-text articles for final inclusion using the software *Rayyan*. Inconsistencies in the list of eligible studies will be resolved through discussion and consensus with the last author (RM).

Data extraction and dealing with missing data

Two authors (JP and LA) will independently extract data from the included studies on a standardised, pre-designed extraction form. In the event of any disagreement between the two authors, a third author (RM) will be consulted. In the case where non-English studies are selected for inclusion in the review, GoogleTranslate will be used to allow for data extraction (18). In the event that data are missing, we will contact the investigators or study sponsors to obtain the missing data. In the event of no reply within one month, we will exclude the study from the outcome respective to the missing data.

The following information will be extracted from the included studies:

- Study characteristics: year of publication, study design, sample size and objectives of study
- Study population: country, WHO region, country income level, hepatitis A vaccination program (yes or no)
- Case definition: clinical case definition and laboratory confirmation methods and the type of virus or viruses indicated as the causative agent for the condition
- Case characteristics: age, gender, hepatitis A vaccination status, country of residence and immune suppressive conditions (e.g. HIV, cancer and diabetes, immunosuppression, chemotherapy)

Data management

Data management will be the responsibility of the first author (JP) in consultation with SS, BMK and RM. An electronic parent folder with the name of this study will be created. Subfolders will also be created to keep the details of different tasks completed such as all records retrieved, records included and excluded, risk of bias assessment results, analyses and full systematic review manuscript drafts. Two back-ups of the parent folder will be created and stored on a memory stick and a hard drive.

Risk of bias assessment of included studies

Two review authors will independently assess the risk of bias for each included study using the Cochrane domain-based evaluation for experimental studies and the 2012 Hoy *et al.,* tool for observational studies (19, 20). In case of disagreement, a third author will be consulted to resolve the inconsistencies. A version of Hot *et al.,* tool is shown in Appendix 1. For included experimental study, we will report bias assessments in the form of a risk of bias graphs created in RevMan (21). For included observational studies, we report risk of bias together with a descriptive summary of the information that influenced our judgment in a risk of bias table. We will judge observational studies as having 'low risk', 'unclear risk' or 'high risk' of bias.

Assessment of heterogeneity

We will use forest plots to assess the presence of statistical heterogeneity. We will assess heterogeneity by calculating Chi^2 (threshold $P > 0.1$) and I^2 statistics (threshold $I^2 > 40\%$). The values of I^2 will be categorized for heterogeneity as follow: "not important" (0 to 40%), "moderate" (41 to 60%) and "considerable" (61 to 80%) and "substantial" (81 to 100%). Where "not important" or "moderate" heterogeneity exists between studies ($I^2 \leq 40\%$), the outcomes will be pooled in a meta-analysis and reported using forest plots. Where "considerable" or "substantial" heterogeneity exists between studies ($I^2 > 40\%$), the outcomes will be reported in narrative form and displayed using forest plots.

Assessment of reporting biases

A funnel plot will be constructed to assess the risk of publication bias included in the meta-analysis with over 10 studies of varying sizes. The funnel plot will be examined for asymmetry visually and statistically using the Egger test (22).

Data synthesis

We will employ STATA software version 14 to analyse the dichotomous data from the included studies through meta-analysis. We will calculate proportions for each outcome with uncertainty in each result expressed using 95% confidence intervals (CI).

Subgroup analysis

Where sufficient data exists, subgroup analyses will be conducted according to the following groupings:

- Age-group
- HIV status (not exposed/not infected, exposed/not-infected, infected)
- Country
- WHO region
- Countries with and without routine hepatitis A vaccination programs

- Length of routine hepatitis A vaccination in a country

Sensitivity analysis

Inclusion/exclusion analyses will be performed in order to assess the potential impact of risk of bias on the robustness of outcome estimates. We will conduct analyses to provide three estimates of intervention effects in respect to bias; outcome estimates with inclusion of only trials at low risk of bias, outcome estimates with inclusion of only trials at high risk of bias and outcome estimates with inclusion of all trials.

Reporting of the review

The study will be presented according to the updated 2009 PRISMA guidelines for reporting systematic reviews. The study selection process will be summarised using a PRISMA flow diagram. Tables will be used to summarise both qualitative and quantitative data from individual studies included in the review. Quantitative data from the review will be presented using narrative descriptions, forest plots and graphs where relevant.

Systematic Review Registration

This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number (CRD42018110309).

Author's contributions

JP, GDH, BK and RM conceived this study. JP developed the study protocol with the help of BK and RM. JP will implement the review under the supervision of RM. JP and LA will perform the study search, screening, and extraction of data under the guidance of RM. SS, LG, WS, MS and GDH will provide content expertise in the review and all authors will provide comments on the final manuscript before publication.

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APPENDIX 1

Table 2: Risk of bias and quality assessment tool for prevalence studies	
External validity	**Score**
1. Was the study's target population a close representation of the national population in relation to relevant variables?	1 Point
2. Was the sampling frame a true or close representation of the target population?	1 point
3. Was some form of random selection used to select the sample, or was a census undertaken?	1 point
4. Was the likelihood of non-response bias minimal?	1 point
Total	**4 points**
Internal validity	**Score**
1. Were data collected directly from the participants (as opposed to a proxy)?	1 point
2. Was an acceptable case definition used in the study?	1 point
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1 point
4. Was the same mode of data collection used for all participants?	1 point
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1 point
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	1 point
Total	**6 points**

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies		
Description of any contact with authors		
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)		
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate		

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results		
Assessment of heterogeneity		
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated		
Provision of appropriate tables and graphics		
Reporting of Results		
Table giving descriptive information for each study included		
Results of sensitivity testing (eg, subgroup analysis)		
Indication of statistical uncertainty of findings		
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)		
Justification for exclusion (eg, exclusion of non–English-language citations)		
Assessment of quality of included studies		
Reporting of Conclusions		
Consideration of alternative explanations for observed results		
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)		
Guidelines for future research		
Disclosure of funding source		

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	7
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	N/A
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	N/A
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	N/A
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	2
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	N/A
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

The Global Epidemiology of Viral-Induced Acute Liver Failure: A Systematic Review Protocol

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Primary Subject Heading:	Epidemiology
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Keywords:	Epidemiology < INFECTIOUS DISEASES, acute liver failure, VIROLOGY

PROTOCOL

The Global Epidemiology of Viral-Induced Acute Liver Failure: A Systematic Review Protocol

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ABSTRACT

Introduction: The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence in general and synthesised data on the relative contribution of different viruses to the aetiology of ALF is missing in the field. The aim of this review is to estimate the burden (prevalence, incidence, mortality, hospitalization) of ALF following infection *HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs.* Establishing the common aetiologies of viral-induced acute liver failure, which vary geographically, is important so that: a) treatment can be initiated quickly, b) contraindications to liver transplant can be identified, c) prognoses can be determined more accurately, and most importantly, d) vaccination against viral ALF aetiologies can be prioritised especially in under-resourced regions with public health risks associated with the relevant attributable diseases.

Methods and analysis: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science databases will be searched for relevant literature published and grey literature from 2009 up to 2019. Published cross-sectional and cohort studies will be eligible for inclusion in this review. Qualifying studies will be formally assessed for quality and risk of bias using a standardised scoring tool. Following standardised data extraction, meta-analyses will be carried out using STATA. Depending on characteristics of included studies, subgroup analyses and meta-regression analyses will be performed. This review will be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Ethics and dissemination: No ethics approval is required as the systematic review will use only published data already in the public domain. Findings will be disseminated through publication in a peer reviewed journal.

Registration: This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42018110309.

Key words: global, epidemiology, acute liver failure

Strengths and limitations of study:

- Comprehensive and exhaustive search for relevant studies from several databases
- Comprehensive diagnostic inclusion criteria for acute liver failure cases according to international guidelines
- Paucity of data may lead to meta-analysis and/or meta-regression analysis not being possible for all global regions
- Diversity of viruses attributable to ALF cases may lead to low statistical power in meta-analysis

MAIN TEXT

INTRODUCTION

Acute liver failure (ALF) refers to a rare syndrome characterised by an acute liver injury resulting in encephalopathy (altered mentation) and coagulopathy (International Normalised Ratio (INR) >1.5) in individuals without known pre-existing liver disease and with an illness of <26 weeks duration (1). The syndrome was originally defined as fulminant liver failure or fulminant hepatic failure in 1970 but was re-defined as ALF in the early 1990s when the understanding of the multiple disease aetiologies, frequency of complications and prognosis of the condition further developed (2). Further sub-classifications of ALF include hyperacute, acute and subacute depending on the time in weeks from the development of jaundice to the development of hepatic encephalopathy (3).

The pathogenesis of ALF includes both direct and immune-mediated liver injury triggered by the disease aetiology (4). The aetiology of ALF determines the clinical course and progression of the disease and well as the need for specific therapy (5). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver diseases (acute fatty liver of pregnancy, HELLP syndrome, preeclampsia), vascular causes (Budd-Chiari syndrome, ischaemic hepatitis) and malignancy (lymphoma, haemophagocytic lymphohistiocytosis). Wilsons disease, vertically-acquired hepatitis B and autoimmune hepatitis are included despite being chronic liver diseases if the diagnosis is made within 26 weeks (6).

Acute viral hepatitis (particularly acute hepatitis A and acute E) has been identified as the most common cause of ALF among all ages in Asia and Africa and the most common causes of ALF in children in Asia and South America (2, 4). The incidence of virally induced ALF has substantially declined in Europe, with only 19% of all ALF cases now related to viral infection (2). Vaccination has led to a significant drop in the incidence of acute hepatitis B induced ALF, with fewer than 4% of ALF cases now attributable to hepatitis B infection in Europe (2). Since the introduction of a universal one-dose hepatitis A vaccination program in Argentina, the number of acute hepatitis A induced ALF cases has decreased from 54.6% to 27.7% (7).

The most common causes of death in patients with ALF are cerebral oedema and multi-organ system failure (4). Mortality rates associated with ALF vary between 60% and 80%, depending on the disease aetiology as well as a patient's access to care (8, 9). Liver transplantation plays a central role in the management of ALF and remains the only definitive treatment for patients who fail to demonstrate spontaneous recovery (1). It remains difficult to predict which patients with ALF will require transplantation and models such as the "Model for End-stage Liver Disease" (MELD) have not improved the accuracy of these predictions (1). The King's College Criteria for emergency liver transplantation remains the most clinically useful, with a sensitivity of 68%-69% and a specificity of 82%-92% (10). Management of ALF cases accounts for 5-12% of all liver transplant activity in the United States and Europe (11). A large proportion of patients with ALF in both high and low resource settings, however, are

deemed to have contraindications to transplantation or deteriorate beyond transplantation before a donor liver is allocated (5, 11, 12).

The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence in general (2). Epidemiological estimates around ALF are based purely on data from transplant units and the medical management of the condition remains poorly defined (1, 2). Establishing the common aetiologies of viral-induced ALF, which vary geographically, is important so that: a) treatment can be initiated quickly, b) contraindications to liver transplant can be identified, c) prognoses can be determined more accurately, and most important, d) vaccination against viral ALF aetiologies can be prioritised especially in under-resourced regions with public health risks associated with the relevant attributable diseases.

To the best of our knowledge, no extensive systematic review of the global epidemiology of viral-induced ALF has previously been conducted. Furthermore, synthesised data on the relative contribution of different viruses to the aetiology of ALF is missing in the field. Hepatitis A is a major cause of ALF and the epidemiology of the disease is changing on a global scale. For example, it has been reported in many low and middle-income countries, that the epidemiology hepatitis A is transitioning from high to intermediate endemicity and this transition is associated with an increasing incidence of acute hepatitis A (13-15). This review aims to describe the global epidemiology of viral-induced ALF.

Aim

To estimate the burden (prevalence, incidence, mortality, hospitalization) of ALF following infection *HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs.*

METHODS

Patient and Public Involvement

This research question was developed as part of an ongoing project by the research team that aims to generate evidence to facilitate evidence-based decision making of introducing routine hepatitis A vaccination in South Africa. The findings of this review will contribute to the knowledge base that aims to enhance global vaccination strategies against viral-associated ALF. As this is a systematic review, no patient involvement will be required; however, it is hoped that the findings of this review will help to highlight the burden that acute liver failure places on populations without routine hepatitis A vaccination. Findings will be disseminated through publication in a peer reviewed journal and included in a technical policy dossier distributed to the National Advisory Group on Immunisation in South Africa.

Criteria for considering studies for this review

Types of studies

Only published cross-sectional, surveillance and cohort studies will be eligible for inclusion in this review.

Types of participants

Patients of any age with any of the following viral infections: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV), coxsackievirus (CA16) and adenovirus (HAdVs).

Case definition

Included studies must have a clearly stated case definition of viral-induced acute liver failure. Cases must be confirmed by both clinical and laboratory diagnostic methods.

- Clinical diagnosis of ALF will be defined as follows for children and adults presenting with an acute liver injury:
    - Children – The absence of known, chronic liver disease with liver-based coagulopathy not responsive to parenteral vitamin K and an international normalised ratio (INR) ≥ 1.5 in the presence of clinical evidence of encephalopathy or INR of ≥ 2.0 without clinical signs of encephalopathy (16)
    - Adults – Liver-based coagulopathy (INR ≥ 1.5) and any grade of hepatic encephalopathy (HE) as defined by the West Haven criteria within 26 weeks after the onset of symptoms but with no evidence of chronic liver disease, including cirrhosis (1, 17)
- Serological, molecular or culture laboratory confirmation of infection with HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 or HAdVs.

Exclusion criteria

Studies will be excluded from this review if they do not report any of the primary outcomes listed or do not match the clearly stated case definition of viral-induced acute liver failure given for this review.

Outcomes

For ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs:

- Prevalence and incidence of ALF
- Mortality rate following ALF
- Prevalence and incidence of requirement for liver transplant
- Mean hospital stay for patients with ALF

Search Methods

The literature search strategy will use both text words and medical subject heading (MeSH) terms (all fields). It will include the following terms: epidemiology, prevalence, incidence, burden, mortality, morbidity, fulminant hepatic failure, fulminant liver failure, acute hepatic failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV) and coxsackie virus. These terms will be adapted for use in each defined database and combined with relevant filters for time period of studies eligible for inclusion in the review. **Table 1** shows an example search strategy for use in PubMed. Each adapted search strategy for use in the outlined databases will be piloted by JP and HH to ensure the outputs retrieved are relevant to the review objectives.

The following electronic databases will be searched from 2009 up to 2019 for relevant published literature: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The starting date of 2009 was chosen as *Bernal et al. 2010* completed searched Medline with the terms “acute liver failure” and “fulminant hepatic failure” between 1997 and 2009, which provided a review of the most relevant publications to practice. No language restriction will be places on the search for studies (8).

Table 1: Search strategy for use in PUBMED

Query	Fields	Search term
#1	All fields	epidemiology OR prevalence OR incidence OR burden OR mortality OR morbidity
#2	All fields	fulminant OR acute
#3	All fields	hepatic failure OR liver failure
#4	All fields	hepatitis a virus OR HAV OR hepatitis b virus OR HBV OR hepatitis c virus OR HCV OR HCV OR hepatitis d virus OR HDV OR hepatitis e virus OR HEV OR epstein-barr virus OR EBV OR herpes simplex virus-1 OR HSV1 OR herpes simplex virus-2 OR HSV2 OR varicella-zoster virus OR VZV OR parvovirus b19 OR human parainfluenza viruses OR yellow fever virus OR YFV OR human herpesvirus 6 OR HHV-6 OR cytomegalovirus OR CMV OR adenovirus OR HAdVs

#5	All fields	humans
#6	N/A	#1 AND #2 AND #3 AND #4 AND #5

Selection of studies

All electronic database outputs will be imported to Rayyan Software for screening and selection. The first and second author will independently screen 100% titles and abstracts for inclusion of potentially eligible trials sourced database searches. Titles and abstracts in non-English languages will be translated into English using Google Translate. HH will collect full-text trials reports/publications of potentially eligible studies and then HH and JP will independently screen 100% of full-text articles for inclusion. Where disagreement may occur between the two authors, the last author (RM) will be consulted. We will record the selection process with reasons for exclusion using a PRISMA flow diagram.

Data extraction and dealing with missing data

Two authors (JP and HH) will independently extract data from the included studies on a standardised, pre-designed extraction form. In the event of any disagreement between the two authors, a third author (RM) will be consulted. In the case where non-English studies are selected for inclusion in the review, GoogleTranslate will be used to allow for data extraction (18). In the event that data are missing, we will contact the investigators or study sponsors to obtain the missing data. In the event of no reply within one month, we will exclude the study from the outcome respective to the missing data. Studies awaiting missing data requests will be marked as "awaiting classification" in the table of included studies.

The following information will be extracted from the included studies:

- Study characteristics: year of publication, study design, sample size and objectives of study
- Study population: country, WHO region, country income level, hepatitis A vaccination program (yes or no)
- Case definition: clinical case definition and laboratory confirmation methods and the type of virus or viruses indicated as the causative agent for the condition
- Case characteristics: age, gender, hepatitis A vaccination status, country of residence and immune suppressive conditions (e.g. HIV, cancer and diabetes, immunosuppression, chemotherapy)

Data management

Data management will be the responsibility of the first author (JP) in consultation with SS, BMK and RM. An electronic parent folder with the name of this study will be created. Subfolders will also be created to keep the details of different tasks completed such as all records retrieved, records included and excluded, risk of bias assessment results, analyses and full systematic review manuscript drafts. Two back-ups of the parent folder will be created and stored on a memory stick and a hard drive.

Risk of bias assessment of included studies

Two review authors will independently assess the risk of bias for each included study using the Cochrane domain-based evaluation for experimental studies and the 2012 Hoy *et al.,* tool for observational studies (19, 20). In case of disagreement, a third author will be consulted to resolve the inconsistencies. A version of *Hoy et al.,* tool is shown in **Appendix 1**. For included experimental study, we will report bias assessments in the form of a risk of bias graphs created in RevMan (21). For included observational studies, we report risk of bias together with a descriptive summary of the information that influenced our judgment in a risk of bias table. We will judge observational studies as having 'low risk', 'unclear risk' or 'high risk' of bias.

Assessment of heterogeneity

We will use forest plots to assess the presence of statistical heterogeneity. We will assess heterogeneity by calculating Chi^2 (threshold $P > 0.1$) and I^2 statistics (threshold $I^2 > 40\%$). The values of I^2 will be categorised for heterogeneity as follow: "not important" (0 to 40%), "moderate" (41 to 60%) and "considerable" (61 to 80%) and "substantial" (81 to 100%). Where "not important" or "moderate" heterogeneity exists between studies ($I^2 \leq 40\%$), the outcomes will be pooled in a meta-analysis and reported using forest plots. Where "considerable" or "substantial" heterogeneity exists between studies ($I^2 > 40\%$), the outcomes will be reported in narrative form and displayed using forest plots.

Assessment of reporting biases

A funnel plot will be constructed to assess the risk of publication bias included in the meta-analysis with over 10 studies of varying sizes. The funnel plot will be examined for asymmetry visually and statistically using the Egger test (22).

Data synthesis

Proportions as percentages will be used to represent measures of frequency prioritised by the primary and secondary outcomes of the review. Included studies for each analysis will be assessed for heterogeneity using the I^2 statistic. Where sufficient homogeneity exists ($I^2 < 50\%$) between studies, data will be pooled in a meta-analysis using Mantel-Haenszel random effects model and an inverse-variance model. Pooled frequency outcome estimates will be presented using forest plots after Freeman-Tukey transformation while comparative effect forest plots will be presented as risk ratios (RR). Both outcome measures will be reported with uncertainty expressed using 95% confidence intervals (CI). Where data are too heterogeneous ($I^2 \geq 50\%$), outcome estimates will be reported narratively. STATA software V.14 (STATA Corporation, College Stations, Texas, USA) will be used to compute all statistical analyses in this review.

Subgroup analysis

Where sufficient data exists, subgroup analyses will be conducted according to the groupings below. Meta-regression analyses will be conducted for all sub-groups where there are ≥ 10 studies for inclusion in the analysis.

- Study design
- Age-groups (1 to 5 years old, 6 to 10 years old, 11 to 15 years old, 16 to 20 years old, 21 to 30 years old, 31 to 40 years old, 41 to 50 years old, 51 to 60 years old, > 60 years old)
    - These age groups have been used as individuals > 60 years old are considered "elderly" in the acute liver failure literature reviewed
- HIV status (not exposed/not infected, exposed/not-infected, infected)
- Country
- WHO region
- Countries with and without routine hepatitis A vaccination programs
- Length of routine hepatitis A vaccination in a country

Sensitivity analysis

Inclusion/exclusion analyses will be performed in order to assess the potential impact of risk of bias on the robustness of outcome estimates. We will conduct analyses to provide three estimates of intervention effects in respect to bias; outcome estimates with inclusion of only studies at low risk of bias, outcome estimates with inclusion of only studies at high risk of bias and outcome estimates with inclusion of all studies. Where inconsistencies exist between outcome estimates with inclusion of only studies at low risk of bias and the outcome estimates of only studies at high risk or all included studies, these inconsistencies will be reported. Further, outcome estimates of studies at low and high risk will be interpreted separately in the review.

Reporting of the review

This review will be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (**Appendix 2**). The study selection process will be summarised using a PRISMA flow diagram. Tables will be used to summarise both qualitative and quantitative data from individual studies included in the review. Quantitative data from the review will be presented using narrative descriptions, forest plots and graphs where relevant.

Systematic Review Registration

This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number (CRD42018110309).

Ethics and dissemination

No ethics approval is required as the systematic review will use only published data already in the public domain. Findings will be disseminated through publication in a peer reviewed journal.

Author's contributions

JP, GDH, BMK and RM conceived this study. JP developed the study protocol with the help of BMK and RM. JP will implement the review under the supervision of RM. JP and HH will perform the study search, screening, and extraction of data under the guidance of RM. LA and BMK will provide methodological expertise for this review. SS, LG, WS, MS and GDH will provide content expertise for this review and all authors will provide comments on the final manuscript before publication. JP will be the guarantor of this review.

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Competing interests

None declared.

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Appendix 1

Hoy et. al **Risk of bias and quality assessment tool for prevalence studies**

External validity	**Score**
1. Was the study's target population a close representation of the national population in relation to relevant variables?	1 Point
2. Was the sampling frame a true or close representation of the target population?	1 point
3. Was some form of random selection used to select the sample, or was a census undertaken?	1 point
4. Was the likelihood of non-response bias minimal?	1 point
Total	**__/4 points**
Internal validity	**Score**
1. Were data collected directly from the participants (as opposed to a proxy)?	1 point
2. Was an acceptable case definition used in the study?	1 point
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1 point
4. Was the same mode of data collection used for all participants?	1 point
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1 point
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	1 point
Total	**__/6 points**

Appendix 2

PRISMA-P Checklist

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 9
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
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	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9

BMJ Open

The Global Epidemiology of Viral-Induced Acute Liver Failure: A Systematic Review Protocol

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Gastroenterology and hepatology, Infectious diseases
Keywords:	Epidemiology < INFECTIOUS DISEASES, acute liver failure, VIROLOGY

PROTOCOL

The Global Epidemiology of Viral-Induced Acute Liver Failure: A Systematic Review Protocol

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ABSTRACT

Introduction: The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence in general and synthesised data on the relative contribution of different viruses to the aetiology of ALF is missing in the field. The aim of this review is to estimate the burden (prevalence, incidence, mortality, hospitalization) of ALF following infection *HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs.* Establishing the common aetiologies of viral-induced acute liver failure, which vary geographically, is important so that: a) treatment can be initiated quickly, b) contraindications to liver transplant can be identified, c) prognoses can be determined more accurately, and most importantly, d) vaccination against viral ALF aetiologies can be prioritised especially in under-resourced regions with public health risks associated with the relevant attributable diseases.

Methods and analysis: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science databases will be searched for relevant literature published and grey literature from 2009 up to 2019. Published cross-sectional and cohort studies will be eligible for inclusion in this review. Qualifying studies will be formally assessed for quality and risk of bias using a standardised scoring tool. Following standardised data extraction, meta-analyses will be carried out using STATA. Depending on characteristics of included studies, subgroup analyses and meta-regression analyses will be performed. This review will be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Ethics and dissemination: No ethics approval is required as the systematic review will use only published data already in the public domain. Findings will be disseminated through publication in a peer reviewed journal.

Registration: This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42018110309.

Key words: global, epidemiology, acute liver failure

Strengths and limitations of study:

- Comprehensive and exhaustive search for relevant studies from several databases
- Comprehensive diagnostic inclusion criteria for acute liver failure cases according to international guidelines
- Paucity of data may lead to meta-analysis and/or meta-regression analysis not being possible for all global regions
- Diversity of viruses attributable to ALF cases may lead to low statistical power in meta-analysis

MAIN TEXT

INTRODUCTION

Acute liver failure (ALF) refers to a rare syndrome characterised by an acute liver injury resulting in encephalopathy (altered mentation) and coagulopathy (International Normalised Ratio (INR) >1.5) in individuals without known pre-existing liver disease and with an illness of <26 weeks duration (1). The syndrome was originally defined as fulminant liver failure or fulminant hepatic failure in 1970 but was re-defined as ALF in the early 1990s when the understanding of the multiple disease aetiologies, frequency of complications and prognosis of the condition further developed (2). Further sub-classifications of ALF include hyperacute, acute and subacute depending on the time in weeks from the development of jaundice to the development of hepatic encephalopathy (3).

The pathogenesis of ALF includes both direct and immune-mediated liver injury triggered by the disease aetiology (4). The aetiology of ALF determines the clinical course and progression of the disease and well as the need for specific therapy (5). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver diseases (acute fatty liver of pregnancy, HELLP syndrome, preeclampsia), vascular causes (Budd-Chiari syndrome, ischaemic hepatitis) and malignancy (lymphoma, haemophagocytic lymphohistiocytosis). Wilsons disease, vertically-acquired hepatitis B and autoimmune hepatitis are included despite being chronic liver diseases if the diagnosis is made within 26 weeks (6).

Acute viral hepatitis (particularly acute hepatitis A and acute E) has been identified as the most common cause of ALF among all ages in Asia and Africa and the most common causes of ALF in children in Asia and South America (2, 4). The incidence of virally induced ALF has substantially declined in Europe, with only 19% of all ALF cases now related to viral infection (2). Vaccination has led to a significant drop in the incidence of acute hepatitis B induced ALF, with fewer than 4% of ALF cases now attributable to hepatitis B infection in Europe (2). Since the introduction of a universal one-dose hepatitis A vaccination program in Argentina, the number of acute hepatitis A induced ALF cases has decreased from 54.6% to 27.7% (7).

The most common causes of death in patients with ALF are cerebral oedema and multi-organ system failure (4). Mortality rates associated with ALF vary between 60% and 80%, depending on the disease aetiology as well as a patient's access to care (8, 9). Liver transplantation plays a central role in the management of ALF and remains the only definitive treatment for patients who fail to demonstrate spontaneous recovery (1). It remains difficult to predict which patients with ALF will require transplantation and models such as the "Model for End-stage Liver Disease" (MELD) have not improved the accuracy of these predictions (1). The King's College Criteria for emergency liver transplantation remains the most clinically useful, with a sensitivity of 68%-69% and a specificity of 82%-92% (10). Management of ALF cases accounts for 5-12% of all liver transplant activity in the United States and Europe (11). A large proportion of patients with ALF in both high and low resource settings, however, are

deemed to have contraindications to transplantation or deteriorate beyond transplantation before a donor liver is allocated (5, 11, 12).

The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence in general (2). Epidemiological estimates around ALF are based purely on data from transplant units and the medical management of the condition remains poorly defined (1, 2). Establishing the common aetiologies of viral-induced ALF, which vary geographically, is important so that: a) treatment can be initiated quickly, b) contraindications to liver transplant can be identified, c) prognoses can be determined more accurately, and most important, d) vaccination against viral ALF aetiologies can be prioritised especially in under-resourced regions with public health risks associated with the relevant attributable diseases.

To the best of our knowledge, no extensive systematic review of the global epidemiology of viral-induced ALF has previously been conducted. Furthermore, synthesised data on the relative contribution of different viruses to the aetiology of ALF is missing in the field. Hepatitis A is a major cause of ALF and the epidemiology of the disease is changing on a global scale. For example, it has been reported in many low and middle-income countries, that the epidemiology hepatitis A is transitioning from high to intermediate endemicity and this transition is associated with an increasing incidence of acute hepatitis A (13-15). This review aims to describe the global epidemiology of viral-induced ALF.

Aim

To estimate the burden (prevalence, incidence, mortality, hospitalization) of ALF following infection *HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs.*

METHODS

Patient and Public Involvement

This research question was developed as part of an ongoing project by the research team that aims to generate evidence to facilitate evidence-based decision making of introducing routine hepatitis A vaccination in South Africa. The findings of this review will contribute to the knowledge base that aims to enhance global vaccination strategies against viral-associated ALF. As this is a systematic review, no patient involvement will be required; however, it is hoped that the findings of this review will help to highlight the burden that acute liver failure places on populations without routine hepatitis A vaccination. Findings will be disseminated through publication in a peer reviewed journal and included in a technical policy dossier distributed to the National Advisory Group on Immunisation in South Africa.

Criteria for considering studies for this review

Types of studies

Only published cross-sectional, surveillance and cohort studies will be eligible for inclusion in this review.

Types of participants

Patients of any age with any of the following viral infections: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV), coxsackievirus (CA16) and adenovirus (HAdVs).

Case definition

Included studies must have a clearly stated case definition of viral-induced acute liver failure. Cases must be confirmed by both clinical and laboratory diagnostic methods.

- Clinical diagnosis of ALF will be defined as follows for children and adults presenting with an acute liver injury:
    - Children – The absence of known, chronic liver disease with liver-based coagulopathy not responsive to parenteral vitamin K and an international normalised ratio (INR) ≥ 1.5 in the presence of clinical evidence of encephalopathy or INR of ≥ 2.0 without clinical signs of encephalopathy (16)
    - Adults – Liver-based coagulopathy (INR ≥ 1.5) and any grade of hepatic encephalopathy (HE) as defined by the West Haven criteria within 26 weeks after the onset of symptoms but with no evidence of chronic liver disease, including cirrhosis (1, 17)
- Serological, molecular or culture laboratory confirmation of infection with HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 or HAdVs.

Exclusion criteria

Studies will be excluded from this review if they do not report any of the primary outcomes listed or do not match the clearly stated case definition of viral-induced acute liver failure given for this review.

Outcomes

For ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs:

- Prevalence and incidence of ALF
- Mortality rate following ALF
- Prevalence and incidence of requirement for liver transplant
- Mean hospital stay for patients with ALF

Search Methods

The literature search strategy will use both text words and medical subject heading (MeSH) terms (all fields). It will include the following terms: epidemiology, prevalence, incidence, burden, mortality, morbidity, fulminant hepatic failure, fulminant liver failure, acute hepatic failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV) and coxsackie virus. These terms will be adapted for use in each defined database and combined with relevant filters for time period of studies eligible for inclusion in the review. **Table 1** shows an example search strategy for use in PubMed. Each adapted search strategy for use in the outlined databases will be piloted by JP and HH to ensure the outputs retrieved are relevant to the review objectives.

The following electronic databases will be searched from 2009 up to 2019 for relevant published literature: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The starting date of 2009 was chosen as *Bernal et al. 2010* completed searched Medline with the terms “acute liver failure” and “fulminant hepatic failure” between 1997 and 2009, which provided a review of the most relevant publications to practice. No language restriction will be places on the search for studies (8).

Table 1: Search strategy for use in PUBMED

Query	Fields	Search term
#1	All fields	epidemiology OR prevalence OR incidence OR burden OR mortality OR morbidity
#2	All fields	fulminant OR acute
#3	All fields	hepatic failure OR liver failure
#4	All fields	hepatitis a virus OR HAV OR hepatitis b virus OR HBV OR hepatitis c virus OR HCV OR HCV OR hepatitis d virus OR HDV OR hepatitis e virus OR HEV OR epstein-barr virus OR EBV OR herpes simplex virus-1 OR HSV1 OR herpes simplex virus-2 OR HSV2 OR varicella-zoster virus OR VZV OR parvovirus b19 OR human parainfluenza viruses OR yellow fever virus OR YFV OR human herpesvirus 6 OR HHV-6 OR cytomegalovirus OR CMV OR adenovirus OR HAdVs

#5	All fields	humans
#6	N/A	#1 AND #2 AND #3 AND #4 AND #5

Selection of studies

All electronic database outputs will be imported to Rayyan Software for screening and selection. The first and second author will independently screen 100% titles and abstracts for inclusion of potentially eligible trials sourced database searches. Titles and abstracts in non-English languages will be translated into English using Google Translate. HH will collect full-text trials reports/publications of potentially eligible studies and then HH and JP will independently screen 100% of full-text articles for inclusion. Where disagreement may occur between the two authors, the last author (RM) will be consulted. We will record the selection process with reasons for exclusion using a PRISMA flow diagram.

Data extraction and dealing with missing data

Two authors (JP and HH) will independently extract data from the included studies on a standardised, pre-designed extraction form. In the event of any disagreement between the two authors, a third author (RM) will be consulted. In the case where non-English studies are selected for inclusion in the review, GoogleTranslate will be used to allow for data extraction (18). In the event that data are missing, we will contact the investigators or study sponsors to obtain the missing data. In the event of no reply within one month, we will exclude the study from the outcome respective to the missing data. Studies awaiting missing data requests will be marked as "awaiting classification" in the table of included studies.

The following information will be extracted from the included studies:

- Study characteristics: year of publication, study design, sample size and objectives of study
- Study population: country, WHO region, country income level, hepatitis A vaccination program (yes or no)
- Case definition: clinical case definition and laboratory confirmation methods and the type of virus or viruses indicated as the causative agent for the condition
- Case characteristics: age, gender, hepatitis A vaccination status, country of residence and immune suppressive conditions (e.g. HIV, cancer and diabetes, immunosuppression, chemotherapy)

Data management

Data management will be the responsibility of the first author (JP) in consultation with SS, BMK and RM. An electronic parent folder with the name of this study will be created. Subfolders will also be created to keep the details of different tasks completed such as all records retrieved, records included and excluded, risk of bias assessment results, analyses and full systematic review manuscript drafts. Two back-ups of the parent folder will be created and stored on a memory stick and a hard drive.

Risk of bias assessment of included studies

Two review authors will independently assess the risk of bias for each included study using the Cochrane domain-based evaluation for experimental studies and the 2012 Hoy *et al.,* tool for observational studies (19, 20). In case of disagreement, a third author will be consulted to resolve the inconsistencies. A version of *Hoy et al.,* tool is shown in **Appendix 1**. For included experimental study, we will report bias assessments in the form of a risk of bias graphs created in RevMan (21). For included observational studies, we report risk of bias together with a descriptive summary of the information that influenced our judgment in a risk of bias table. We will judge observational studies as having 'low risk', 'unclear risk' or 'high risk' of bias.

Assessment of heterogeneity

We will use forest plots to assess the presence of statistical heterogeneity. We will assess heterogeneity by calculating Chi^2 (threshold $P > 0.1$) and I^2 statistics (threshold $I^2 > 40\%$). The values of I^2 will be categorised for heterogeneity as follow: "not important" (0 to 40%), "moderate" (41 to 60%) and "considerable" (61 to 80%) and "substantial" (81 to 100%). Where "not important" or "moderate" heterogeneity exists between studies ($I^2 \leq 40\%$), the outcomes will be pooled in a meta-analysis and reported using forest plots. Where "considerable" or "substantial" heterogeneity exists between studies ($I^2 > 40\%$), the outcomes will be reported in narrative form and displayed using forest plots.

Assessment of reporting biases

A funnel plot will be constructed to assess the risk of publication bias included in the meta-analysis with over 10 studies of varying sizes. The funnel plot will be examined for asymmetry visually and statistically using the Egger test (22).

Data synthesis

Proportions as percentages will be used to represent measures of frequency prioritised by the primary and secondary outcomes of the review. Included studies for each analysis will be assessed for heterogeneity using the I^2 statistic. Where sufficient homogeneity exists ($I^2 < 50\%$) between studies, data will be pooled in a meta-analysis. 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. Both outcome measures will be reported with uncertainty expressed using 95% confidence intervals (CI). Where data are too heterogeneous ($I^2 \geq 50\%$),

outcome estimates will be reported narratively. STATA software V.14 (STATA Corporation, College Stations, Texas, USA) will be used to compute all statistical analyses in this review.

Subgroup analysis

Where sufficient data exists, subgroup analyses will be conducted according to the groupings below. Meta-regression analyses will be conducted for all sub-groups where there are ≥ 10 studies for inclusion in the analysis.

- Study design
- Age-groups (1 to 5 years old, 6 to 10 years old, 11 to 15 years old, 16 to 20 years old, 21 to 30 years old, 31 to 40 years old, 41 to 50 years old, 51 to 60 years old, > 60 years old)
    - These age groups have been used as individuals > 60 years old are considered "elderly" in the acute liver failure literature reviewed
- HIV status (not exposed/not infected, exposed/not-infected, infected)
- Country
- WHO region
- Countries with and without routine hepatitis A vaccination programs
- Length of routine hepatitis A vaccination in a country

Sensitivity analysis

Inclusion/exclusion analyses will be performed in order to assess the potential impact of risk of bias on the robustness of outcome estimates. We will conduct analyses to provide three estimates of intervention effects in respect to bias; outcome estimates with inclusion of only studies at low risk of bias, outcome estimates with inclusion of only studies at high risk of bias and outcome estimates with inclusion of all studies. Where inconsistencies exist between outcome estimates with inclusion of only studies at low risk of bias and the outcome estimates of only studies at high risk or all included studies, these inconsistencies will be reported. Further, outcome estimates of studies at low and high risk will be interpreted separately in the review.

Reporting of the review

This review will be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (**Appendix 2**). The study selection process will be summarised using a PRISMA flow diagram. Tables will be used to summarise both qualitative and quantitative data from individual studies included in the review. Quantitative data from the review will be presented using narrative descriptions, forest plots and graphs where relevant.

Systematic Review Registration

This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number (CRD42018110309).

Ethics and dissemination

No ethics approval is required as the systematic review will use only published data already in the public domain. Findings will be disseminated through publication in a peer reviewed journal.

Author's contributions

JP, GDH, BMK and RM conceived this study. JP developed the study protocol with the help of BMK and RM. JP will implement the review under the supervision of RM. JP and HH will perform the study search, screening, and extraction of data under the guidance of RM. LA and BMK will provide methodological expertise for this review. SS, LG, WS, MS and GDH will provide content expertise for this review and all authors will provide comments on the final manuscript before publication. JP will be the guarantor of this review.

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Competing interests

None declared.

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Appendix 1

Hoy et. al **Risk of bias and quality assessment tool for prevalence studies**

External validity	**Score**
1. Was the study's target population a close representation of the national population in relation to relevant variables?	1 Point
2. Was the sampling frame a true or close representation of the target population?	1 point
3. Was some form of random selection used to select the sample, or was a census undertaken?	1 point
4. Was the likelihood of non-response bias minimal?	1 point
Total	**__/4 points**
Internal validity	**Score**
1. Were data collected directly from the participants (as opposed to a proxy)?	1 point
2. Was an acceptable case definition used in the study?	1 point
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1 point
4. Was the same mode of data collection used for all participants?	1 point
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1 point
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	1 point
Total	**__/6 points**

Appendix 2

PRISMA-P Checklist

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 9
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9