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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

# SCHOLARONE<sup>™</sup> Manuscripts

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 Published and unpublished case-series, cross-sectional, cohort and randomised control trials (RCT) and non-randomised control trials (nRCT) will be eligible for inclusion in this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

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#### 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 underresourced 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

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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 nonrandomized 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

1 2 3	
4 5 6	
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19 20 21 22	
22 23 24 25	
26 27 28	
29 30 31	
29 30 31 32 33 34 35 36 37	
36 37 38	
39 40 41	
42 43 44	
45 46 47	
48 49 50	
51 52 53 54	
54 55 56 57	
58 59 60	

#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 domainbased 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<sup>2</sup> (threshold P > 0.1) and I<sup>2</sup> statistics (threshold I<sup>2</sup> > 40%). The values of I<sup>2</sup> 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<sup>2</sup>  $\leq$  40%), the outcomes will be pooled in a meta-analysis and reported using forest plots. Where "considerable" or "substantial" heterogeneity exists between studies (I<sup>2</sup> > 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

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• 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 low risk of bias.

#### 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

<ul> <li>4. Was the likelihood of non-response bias minimal?</li> <li>Total Internal validity </li> <li>1. Were data collected directly from the participants (as opposed to a proxy)? </li> <li>2. Was an acceptable case definition used in the study?</li> <li>3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?</li></ul>	1 Point 1 point 1 point 1 point 4 points Score
<ul> <li>3. Was some form of random selection used to select the sample, or was a census undertaken?</li> <li>4. Was the likelihood of non-response bias minimal?</li> <li>Total Internal validity </li> <li>1. Were data collected directly from the participants (as opposed to a proxy)? </li> <li>2. Was an acceptable case definition used in the study?</li> <li>3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?</li></ul>	1 point 1 point 4 points
<ul> <li>4. Was the likelihood of non-response bias minimal?</li> <li>Total Internal validity </li> <li>1. Were data collected directly from the participants (as opposed to a proxy)? </li> <li>2. Was an acceptable case definition used in the study?</li> <li>3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?</li></ul>	1 point 4 points
Total       Internal validity         1. Were data collected directly from the participants (as opposed to a proxy)?         2. Was an acceptable case definition used in the study?         3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	4 points
<ol> <li>Were data collected directly from the participants (as opposed to a proxy)?</li> <li>Was an acceptable case definition used in the study?</li> <li>Was the study instrument that measured the parameter of interest shown to have validity and reliability?</li> </ol>	
<ol> <li>Were data collected directly from the participants (as opposed to a proxy)?</li> <li>Was an acceptable case definition used in the study?</li> <li>Was the study instrument that measured the parameter of interest shown to have validity and reliability?</li> </ol>	Score
<ol> <li>Was an acceptable case definition used in the study?</li> <li>Was the study instrument that measured the parameter of interest shown to have validity and reliability?</li> </ol>	
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1 point
	1 point
	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		

1	Reporting Criteria	Reported (Yes/No)	Reported on Page No.
ן ר	Assessment of study quality, including		
2 3	blinding of quality assessors;		
4	stratification or regression on possible		
5	predictors of study results		
6	Assessment of heterogeneity		
7	Description of statistical methods (eg,		
3	complete description of fixed or random		
9	effects models, justification of whether		
0	the chosen models account for predictors		
12	of study results, dose-response models,		
13			
4	or cumulative meta-analysis) in sufficient		
5	detail to be replicated		
16	Provision of appropriate tables and		
17	graphics		
8	Reporting of Results		
19	Table giving descriptive information for		
20 21	each study included		
22	Results of sensitivity testing (eg,		
23	subgroup analysis)		
24	Indication of statistical uncertainty of		
5	findings		
6	Reporting of Discussion		
7	Quantitative assessment of bias (eg,	4	
.8 .9	publication bias)		
.9 10	Justification for exclusion (eg, exclusion		
80 81	of non–English-language citations)		
52			
3	Assessment of quality of included studies		
4	Reporting of Conclusions		
85	Consideration of alternative explanations		
36	for observed results		
37	Generalization of the conclusions (ie,		
38 39	appropriate for the data presented and		
40	within the domain of the literature review)		
40	Guidelines for future research		
42	Disclosure of funding source		
43			

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.

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# PRISMA 2009 Checklist

#	Checklist item	Reported on page #
1	Identify the report as a systematic review, meta-analysis, or both.	7
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
3	Describe the rationale for the review in the context of what is already known.	4
4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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
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
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
8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
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
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
11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
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
13	State the principal summary measures (e.g., risk ratio, difference in means).	8
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
	1         2         3         3         4         5         6         7         8         9         10         11         12         13	1       Identify the report as a systematic review, meta-analysis, or both.         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.         3       Describe the rationale for the review in the context of what is already known.         4       Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).         5       Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration number.         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.         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.         8       Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.         9       State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).         10       Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming d



# **PRISMA 2009 Checklist**

<ul> <li>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</li> <li>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</li> <li>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.</li> <li>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</li> </ul>	8 8 N/A
<ul> <li>which were pre-specified.</li> <li>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.</li> <li>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and</li> </ul>	
<ul> <li>each stage, ideally with a flow diagram.</li> <li>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and</li> </ul>	N/A
<ul> <li>each stage, ideally with a flow diagram.</li> <li>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and</li> </ul>	N/A
provide the citations.	N/A
Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
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
Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
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
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
Provide a general interpretation of the results in the context of other evidence, and implications for future research.	N/A
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
	<ul> <li>intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</li> <li>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</li> <li>Present results of any assessment of risk of bias across studies (see Item 15).</li> <li>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</li> <li>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).</li> <li>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).</li> <li>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</li> <li>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the</li> </ul>

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2019-029819.R1
Article Type:	Protocol
Date Submitted by the Author:	20-May-2019
Complete List of Authors:	Patterson, Jenna; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Hussey, Hannah; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Abdullahi, Leila; Save the Children International, Research, Evaluation, Analysis, Learning and Monitoring (REALM) Silal, Sheetal; University of Cape Town, Department of Statistical Sciences; University of Oxford, Nuffield Department of Medicine Goddard, Liz; University of Cape Town, Department of Paediatrics, Red Cross War Memorial Children's Hospital Setshedi, Mashiko; University of Cape Town, Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital Spearman, Wendy ; University of Cape Town, Department of Medicine, Division of Hepatology, Groote Schuur Hospital Hussey, Gregory; University of Cape Town, School of Public Health & Family Medicine, Vaccines For Africa Initiative; University of Cape Town, Institute of Infectious Disease and Molecular Medicine Kagina, Benjamin; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Muloiwa, Rudzani; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Muloiwa, Rudzani; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Muloiwa, Rudzani; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Muloiwa, Rudzani; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative; University of Cape Town, Department of Paediatrics, Groote Schuur Hospital
<b>Primary Subject Heading</b> :	Epidemiology
Secondary Subject Heading:	Gastroenterology and hepatology, Infectious diseases
Keywords:	Epidemiology < INFECTIOUS DISEASES, acute liver failure, VIROLOGY

# SCHOLARONE<sup>™</sup> Manuscripts

1 2		
3 4	1	PROTOCOL
5 6	2	
7 8	3 4	The Global Epidemiology of Viral-Induced Acute Liver Failure: A Systematic Review Protocol
9 10	5	Jenna Patterson <sup>1,2</sup> , Hannah Hussey <sup>1,2</sup> , Leila Abdullahi <sup>2.4</sup> , Sheetal Silal <sup>5</sup> , Liz Goddard <sup>6</sup> , Mashiko
11 12	6	Setshedi <sup>7</sup> , Wendy Spearman <sup>7</sup> , Gregory D. Hussey <sup>1,8</sup> , Benjamin M. Kagina <sup>1,2</sup> and Rudzani
13 14	7	Muloiwa <sup>1,6</sup>
15	8	
16 17	9	
18	10	
19 20	11	
21	12	
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32	19	<sup>6</sup> Department of Paediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town
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58 59 60		Patterson, J et al. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

2 3	34	ABSTRACT
4 5	35	Introduction: The burden of viral-induced ALF around the world still remains unclear, with little to no data
6	36	collected regarding the disease incidence in general and synthesised data on the relative contribution of different
7 8	37	viruses to the aetiology of ALF is missing in the field. The aim of this review is to estimate the burden (prevalence,
9	38	incidence, mortality, hospitalization) of ALF following infection HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV,
10 11	39	parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs. Establishing the common aetiologies of viral-
12	40	induced acute liver failure, which vary geographically, is important so that: a) treatment can be initiated quickly, b)
13 14	41	contraindications to liver transplant can be identified, c) prognoses can be determined more accurately, and most
15 16	42	importantly, d) vaccination against viral ALF aetiologies can be prioritised especially in under-resourced regions
17	43	with public health risks associated with the relevant attributable diseases.
18 19	44	
20	45	Methods and analysis: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science databases will be searched
21 22	46	for relevant literature published and grey literature from 2009 up to 2019. Published cross-sectional and cohort
23	47	studies will be eligible for inclusion in this review. Qualifying studies will be formally assessed for quality and risk of
24 25	48	bias using a standardised scoring tool. Following standardised data extraction, meta-analyses will be carried out
26	49	using STATA. Depending on characteristics of included studies, subgroup analyses and meta-regression analyses
27 28	50	will be performed. This review will be reported according to Preferred Reporting Items for Systematic reviews and
29	51	Meta-Analyses (PRISMA) guidelines.
30 31	52	
32 33	53	Ethics and dissemination: No ethics approval is required as the systematic review will use only published data
33 34	54	already in the public domain. Findings will be disseminated through publication in a peer reviewed journal.
35 36	55	
37	56	Registration: This protocol has been registered with the International Prospective Register of Systematic Reviews
38 39	57	(PROSPERO), registration number CRD42018110309.
40	58	
41 42	59	Key words: global, epidemiology, acute liver failure
43	60	
44 45	61	Strengths and limitations of study:
46	62	Comprehensive and exhaustive search for relevant studies from several databases
47 48	63	Comprehensive diagnostic inclusion criteria for acute liver failure cases according to international
49 50	64	guidelines
50 51	65	• Paucity of data may lead to meta-analysis and/or meta-regression analysis not being possible for all global
52 53	66	regions
54	67	• Diversity of viruses attributable to ALF cases may lead to low statistical power in meta-analysis
55 56	68	
57		2
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2		
3 4	69	MAIN TEXT
5	70	INTRODUCTION
6 7	71	Acute liver failure (ALF) refers to a rare syndrome characterised by an acute liver injury resulting in encephalopathy
8	72	(altered mentation) and coagulopathy (International Normalised Ratio (INR) >1.5 ) in individuals without known
9 10	73	pre-existing liver disease and with an illness of <26 weeks duration (1). The syndrome was originally defined as
11	74	fulminant liver failure or fulminant hepatic failure in 1970 but was re-defined as ALF in the early 1990s when the
12 13	75	understanding of the multiple disease aetiologies, frequency of complications and prognosis of the condition
14	76	further developed (2). Further sub-classifications of ALF include hyperacute, acute and subacute depending on the
15 16	77	time in weeks from the development of jaundice to the development of hepatic encephalopathy (3).
17	78	
18 19	79	The pathogenesis of ALF includes both direct and immune-mediated liver injury triggered by the disease aetiology
20	80	(4). The aetiology of ALF determines the clinical course and progression of the disease and well as the need for
21 22	81	specific therapy (5). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver
23	82	diseases (acute fatty liver of pregnancy, HELLP syndrome, preeclampsia), vascular causes (Budd-Chiari syndrome,
24 25	83	ischaemic hepatitis) and malignancy (lymphoma, haemophagocytic lymphohistiocytosis). Wilsons disease,
26	84	vertically-acquired hepatitis B and autoimmune hepatitis are included despite being chronic liver diseases if the
27 28	85	diagnosis is made within 26 weeks (6).
29	86	
30 31	87	Acute viral hepatitis (particularly acute hepatitis A and acute E) has been identified as the most common cause of
32	88	ALF among all ages in Asia and Africa and the most common causes of ALF in children in Asia and South America (2,
33 34	89	4). The incidence of virally induced ALF has substantially declined in Europe, with only 19% of all ALF cases now
35	90	related to viral infection (2). Vaccination has led to a significant drop in the incidence of acute hepatitis B induced
36 37	91	ALF, with fewer than 4% of ALF cases now attributable to hepatitis B infection in Europe (2). Since the introduction
38	92	of a universal one-dose hepatitis A vaccination program in Argentina, the number of acute hepatitis A induced ALF
39 40	93	cases has decreased from 54.6% to 27.7% (7).
41		
42 43	94	The most common causes of death in patients with ALF are cerebral oedema and multi-organ system failure (4).
44	95	Mortality rates associated with ALF vary between 60% and 80%, depending on the disease aetiology as well as a
45 46	96	patient's access to care (8, 9). Liver transplantation plays a central role in the management of ALF and remains the
47	97	only definitive treatment for patients who fail to demonstrate spontaneous recovery (1). It remains difficult to
48 49	98	predict which patients with ALF will require transplantation and models such as the "Model for End-stage Liver
50	99	Disease" (MELD) have not improved the accuracy of these predictions (1). The King's College Criteria for
51 52	100	emergency liver transplantation remains the most clinically useful, with a sensitivity of 68%-69% and a specificity
53	101	of 82%-92% (10). Management of ALF cases accounts for 5-12% of all liver transplant activity in the United States
54 55	102	and Europe (11). A large proportion of patients with ALF in both high and low resource settings, however, are
56		
57 50		3

deemed to have contraindications to transplantation or deteriorate beyond transplantation before a donor liver is

1 2 3

4	105	decined to have contraindications to transplantation of deteriorate beyond transplantation before a donor inversi
4 5 6	104	allocated (5, 11, 12).
7 8	105	The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding
9	106	the disease incidence in general (2). Epidemiological estimates around ALF are based purely on data from
10 11	107	transplant units and the medical management of the condition remains poorly defined (1, 2). Establishing the
12	108	common aetiologies of viral-induced ALF, which vary geographically, is important so that: a) treatment can be
13 14	109	initiated quickly, b) contraindications to liver transplant can be identified, c) prognoses can be determined more
15	110	accurately, and most important, d) vaccination against viral ALF aetiologies can be prioritised especially in under-
16 17	111	resourced regions with public health risks associated with the relevant attributable diseases.
18	112	
19 20	113	To the best of our knowledge, no extensive systematic review of the global epidemiology of viral-induced ALF has
21	114	previously been conducted. Furthermore, synthesised data on the relative contribution of different viruses to the
22 23	115	aetiology of ALF is missing in the field. Hepatitis A is a major cause of ALF and the epidemiology of the disease is
24	116	changing on a global scale. For example, it has been reported in many low and middle-income countries, that the
25 26	117	epidemiology hepatitis A is transitioning from high to intermediate endemicity and this transition is associated
27 20	118	with an increasing incidence of acute hepatitis A (13-15). This review aims to describe the global epidemiology of
28 29	119	viral-induced ALF.
30 31	120	
32	121	Aim
33 34	122	To estimate the burden (prevalence, incidence, mortality, hospitalization) of ALF following infection HAV, HBV,
35	123	HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs.
36 37	124	
38	125	METHODS
39 40	126	Patient and Public Involvement
41	127	This research question was developed as part of an ongoing project by the research team that aims to generate
42 43	128	evidence to facilitate evidence-based decision making of introducing routine hepatitis A vaccination in South
44	129	Africa. The findings of this review will contribute to the knowledge base that aims to enhance global vaccination
45 46	130	strategies against viral-associated ALF. As this is a systematic review, no patient involvement will be required;
47	131	however, it is hoped that the findings of this review will help to highlight the burden that acute liver failure places
48 49	132	on populations without routine hepatitis A vaccination. Findings will be disseminated through publication in a peer
50	133	reviewed journal and included in a technical policy dossier distributed to the National Advisory Group on
51 52	134	Immunisation in South Africa.
53	135	
54 55	136	
56 57		
58		4
59 60		Patterson, J et al. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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1 2		
3	137	Criteria for considering studies for this review
4 5	138	Types of studies
6 7	139	Only published cross-sectional, surveillance and cohort studies will be eligible for inclusion in this review.
8	140	
9 10	141	Types of participants
10	142	Patients of any age with any of the following viral infections: hepatitis A virus (HAV), hepatitis B virus (HBV),
12 13	143	hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes simplex
13	144	virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza
15 16	145	viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV), coxsackievirus
17	146	(CA16) and adenovirus (HAdVs).
18 19	147	
20	148	Case definition
21 22	149	Included studies must have a clearly stated case definition of viral-induced acute liver failure. Cases must be
23	150	confirmed by both clinical and laboratory diagnostic methods.
24 25	151	• Clinical diagnosis of ALF will be defined as follows for children and adults presenting with an acute liver
26	152	injury:
27 28	153	• Children – The absence of known, chronic liver disease with liver-based coagulopathy not
29	154	responsive to parenteral vitamin K and an international normalised ratio (INR) $\ge$ 1.5 in the
30 31	155	presence of clinical evidence of encephalopathy or INR of $\geq$ 2.0 without clinical signs of
32	156	encephalopathy (16)
33 34	157	<ul> <li>Adults – Liver-based coagulopathy (INR ≥ 1.5) and any grade of hepatic encephalopathy (HE) as</li> </ul>
35	158	defined by the West Haven criteria within 26 weeks after the onset of symptoms but with no
36 37	159	evidence of chronic liver disease, including cirrhosis (1, 17)
38	160	• Serological, molecular or culture laboratory confirmation of infection with HAV, HBV, HCV, HDV, HEV,
39 40	161	EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 or HAdVs.
41	162	
42 43	163	Exclusion criteria
44 45	164	Studies will be excluded from this review if they do not report any of the primary outcomes listed or do not match
45 46	165	the clearly stated case definition of viral-induced acute liver failure given for this review.
47 48	166	
48 49	167	
50	168	
51 52	169	
53 54	170	
54 55	171	
56 57		_
58		5
59 60		Patterson, J et al. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
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$\begin{array}{c} 1\\ 2\\ 3\\ 4\\ 5\\ 6\\ 7\\ 8\\ 9\\ 10\\ 11\\ 23\\ 14\\ 15\\ 16\\ 17\\ 18\\ 9\\ 20\\ 21\\ 22\\ 32\\ 4\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 5\\ 36\\ 37\\ 38\\ 9\\ 40\\ 41\\ 42\\ 43\\ 44\\ 5\\ 46\\ 47\\ 46\\ 47\\ 45\\ 46\\ 47\\ 45\\ 46\\ 47\\ 46\\ 46\\ 47\\ 46\\ 46\\ 47\\ 46\\ 46\\ 47\\ 46\\ 46\\ 47\\ 46\\ 46\\ 47\\ 46\\ 46\\ 47\\ 46\\ 46\\ 46\\ 46\\ 46\\ 47\\ 46\\ 46\\ 46\\ 47\\ 46\\ 46\\ 46\\ 46\\ 4$	172			
	173	Outcom	es	
	174	For ALF	following	infection with HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV,
$\begin{array}{c} 2\\ 3\\ 4\\ 5\\ 6\\ 7\\ 8\\ 9\\ 10\\ 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 5\\ 36\\ 37\\ 38\\ 39\\ 40\\ 142\\ 43\\ 445\\ 46\\ 47\\ 48\end{array}$	175	HVV-6, (	CMV, CA16	5 and/or HAdVs:
	176	•	Prevalenc	ce and incidence of ALF
11	177	٠	Mortality	rate following ALF
	178	•	Prevalence	ce and incidence of requirement for liver transplant
14	179	•	Mean ho	spital stay for patients with ALF
14 15 16 17 18 19 20 21 22	180			
7	181	Search I	Methods	
	182	The liter	ature sear	rch strategy will use both text words and medical subject heading (MeSH) terms (all fields). It will
	183	include	the follow	ing terms: epidemiology, prevalence, incidence, burden, mortality, morbidity, fulminant hepatic
	184	failure, f	ulminant	liver failure, acute hepatic failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus
	185	(HBV), h	epatitis C	virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes
	186	simplex	virus-1 (H	SV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human
	187	parainflu	uenza viru	ses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV) and
27 28 29	188	coxsacki	e virus. Th	nese terms will be adapted for use in each defined database and combined with relevant filters
	189	for time	period of	studies eligible for inclusion in the review. <b>Table 1</b> shows an example search strategy for use in
	190	PubMed	l. Each ada	apted search strategy for use in the outlined databases will be piloted by JP and HH to ensure the
	191	outputs	retrieved	are relevant to the review objectives.
34	192			
	193	The follo	owing elec	tronic databases will be searched from 2009 up to 2019 for relevant published literature:
	194	EBSCOh	ost, PubM	ed, ScienceDirect, Scopus and Web of Science. The starting date of 2009 was chosen as Bernal et
	195	al. 2010	complete	d searched Medline with the terms "acute liver failure" and "fulminant hepatic failure" between
40	196	1997 an	d 2009, wl	hich provided a review of the most relevant publications to practice. No language restriction will
	197	be place	s on the s	earch for studies (8).
43	198			
		Table 1 Query	L: Search stra	ategy for use in PUBMED
46		#1	All fields	epidemiology OR prevalence OR incidence OR burden OR mortality OR morbidity
49		#2	All fields	fulminant OR acute
50 51		#3	All fields	hepatic failure OR liver failure
52 53 54		#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

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	#5	All fields	humans					
	#6	N/A	#1 AND #2 AND #3 AND #4 AND #5					
99		ion of studie						
)		-	base outputs will be imported to Rayyan Software for screening and selection. The first and					
	second	d author will	independently screen 100% titles and abstracts for inclusion of potentially eligible trials sou	rced				
2	databa	ase searches	. Titles and abstracts in non-English languages will be translated into English using Google					
3	Transla	ate. HH will	collect full-text trials reports/publications of potentially eligible studies and then HH and JP v	vill				
4	indepe	endently scr	een 100% of full-text articles for inclusion. Where disagreement may occur between the two					
)5	author	rs, the last a	uthor (RM) will be consulted. We will record the selection process with reasons for exclusion	I				
)6	using a	a PRISMA flo	ow diagram.					
07								
)8	nd dealing with missing data							
)9	Two a	uthors (JP ar	nd HH) will independently extract data from the included studies on a standardised, pre-desig	gned				
10	extrac	tion form. Ir	the event of any disagreement between the two authors, a third author (RM) will be consul	ted.				
11	In the	case where	non-English studies are selected for inclusion in the review, GoogleTranslate will be used to					
12	allow f	for data extr	action (18). In the event that data are missing, we will contact the investigators or study					
213	sponse	sponsors to obtain the missing data. In the event of no reply within one month, we will exclude the study from the						
214	outcor	outcome respective to the missing data. Studies awaiting missing data requests will be marked as "awaiting						
15	classifi	classification" in the table of included studies.						
16								
17	The fo	llowing info	rmation will be extracted from the included studies:					
8	• St	udy charact	eristics: year of publication, study design, sample size and objectives of study					
9	• St	udy populat	ion: country, WHO region, country income level, hepatitis A vaccination program (yes or no)					
20	• Ca	ase definitio	n: clinical case definition and laboratory confirmation methods and the type of virus or virus	es				
21	in	dicated as t	ne causative agent for the condition					
22	• Ca	ase characte	ristics: age, gender, hepatitis A vaccination status, country of residence and immune suppres	ssive				
23	сс	onditions (e.	g. HIV, cancer and diabetes, immunosuppression, chemotherapy)					
24								
25	Data n	managemen	t					
26	Data n	nanagement	will be the responsibility of the first author (JP) in consultation with SS, BMK and RM. An					
27	electro	onic parent f	older with the name of this study will be created. Subfolders will also be created to keep the	2				
28	details	of different	tasks completed such as all records retrieved, records included and excluded, risk of bias					
29	assess	ment result	s, analyses and full systematic review manuscript drafts. Two back-ups of the parent folder w	/ill				
30	be cre	ated and sto	pred on a memory stick and a hard drive.					
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3	232		
4 5	233		
6	234	Risk of bias assessment of included studies	
7 8	235	Two review authors will independently assess the risk of bias for each included study using the Cochrane domain	1-
9 10	236	based evaluation for experimental studies and the 2012 Hoy et al., tool for observational studies (19, 20). In case	ì
10	237	of disagreement, a third author will be consulted to resolve the inconsistencies. A version of Hoy et al., tool is	
12 13	238	shown in Appendix 1. For included experimental study, we will report bias assessments in the form of a risk of bi	as
14	239	graphs created in RevMan (21). For included observational studies, we report risk of bias together with a	
15 16	240	descriptive summary of the information that influenced our judgment in a risk of bias table. We will judge	
17	241	observational studies as having 'low risk', 'unclear risk' or 'high risk' of bias.	
18 19	242		
20	243	Assessment of heterogeneity	
21 22	244	We will use forest plots to assess the presence of statistical heterogeneity. We will assess heterogeneity by	
23	245	calculating Chi <sup>2</sup> (threshold P > 0.1) and I <sup>2</sup> statistics (threshold I <sup>2</sup> > 40%). The values of I <sup>2</sup> will be categorised for	
24 25	246	heterogeneity as follow: "not important" (0 to 40%), "moderate" (41 to 60%) and "considerable" (61 to 80%) and	ł
26	247	"substantial" (81 to 100%). Where "not important" or "moderate" heterogeneity exists between studies (I $^2 \leq$	
27 28	248	40%), the outcomes will be pooled in a meta-analysis and reported using forest plots. Where "considerable" or	
29	249	"substantial" heterogeneity exists between studies (I <sup>2</sup> > 40%), the outcomes will be reported in narrative form ar	nd
30 31	250	displayed using forest plots.	
32	251		
33 34	252	Assessment of reporting biases	
35	253	A funnel plot will be constructed to assess the risk of publication bias included in the meta-analysis with over 10	
36 37	254	studies of varying sizes. The funnel plot will be examined for asymmetry visually and statistically using the Egger	
38 39	255	test (22).	
39 40	256		
41 42	257	Data synthesis	
43	258	Proportions as percentages will be used to represent measures of frequency prioritised by the primary and	
44 45	259	secondary outcomes of the review. Included studies for each analysis will be assessed for heterogeneity using the	e
46	260	$I^2$ statistic. Where sufficient homogeneity exists ( $I^2 < 50$ %) between studies, data will be pooled in a meta-	
47 48	261	analysis using Mantel-Haenszel random effects model and an inverse-variance model. Pooled frequency outcome	e
49	262	estimates will be presented using forest plots after Freeman-Tukey transformation while comparative effect fore	est
50 51	263	plots will be presented as risk ratios (RR). Both outcome measures will be reported with uncertainty expressed	
52	264	using 95% confidence intervals (CI). Where data are too heterogeneous ( $I^2 \ge 50\%$ ), outcome estimates will be	
53 54	265	reported narratively. STATA software V.14 (STATA Corporation, College Stations, Texas, USA) will be used to	
55	266	compute all statistical analyses in this review.	
56 57			8
58 59		Patterson, J et al. For peer review only - http://bmiopen.bmi.com/site/about/guidelines.xhtml	U

1 2							
3	267						
4 5	268						
6	269	Subgroup analysis					
7 8	270	Where sufficient data exists, subgroup analyses will be conducted according to the groupings below. Meta-					
9	271	regression analyses will be conducted for all sub-groups where there are $\geq$ 10 studies for inclusion in the analys	is.				
10 11	272	Study design					
12 13	273	• 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,					
14	274	31 to 40 years old, 41 to 50 years old, 51 to 60 years old, $> 60$ years old)					
15 16 17	275 276	<ul> <li>These age groups have been used as individuals &gt; 60 years old are considered "elderly" in the acute liver failure literature reviewed</li> </ul>	ĩ				
18 10	277	HIV status (not exposed/not infected, exposed/not-infected, infected)					
19 20 21 22	278	• Country					
	279	WHO region					
23	280	Countries with and without routine hepatitis A vaccination programs					
24 25	281	Length of routine hepatitis A vaccination in a country					
26 27	282						
27 28	283	Sensitivity analysis					
29 30	284	Inclusion/exclusion analyses will be performed in order to assess the potential impact of risk of bias on the					
31	285	robustness of outcome estimates. We will conduct analyses to provide three estimates of intervention effects in					
32 33	286	respect to bias; outcome estimates with inclusion of only studies at low risk of bias, outcome estimates with					
34	287	inclusion of only studies at high risk of bias and outcome estimates with inclusion of all studies. Where					
35 36	288	inconsistencies exist between outcome estimates with inclusion of only studies at low risk of bias and the outcon	۱e				
37	289	estimates of only studies at high risk or all included studies, these inconsistencies will be reported. Further,					
38 39	290	outcome estimates of studies at low and high risk will be interpreted separately in the review.					
40 41	291						
42	292	Reporting of the review					
43 44	293	This review will be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses					
45	294	(PRISMA) guidelines ( <b>Appendix 2</b> ). The study selection process will be summarised using a PRISMA flow diagram.					
46 47	295 206	Tables will be used to summarise both qualitative and quantitative data from individual studies included in the					
48	296	review. Quantitative data from the review will be presented using narrative descriptions, forest plots and graphs					
49 50	297	where relevant.					
51 52	298						
53	299 200	Systematic Review Registration					
54 55	300	This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO)					
56	301	registration number (CRD42018110309).					
57 58			9				
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3 4	302		
4 5	303		
6 7	304	Ethics and dissemination	
8	305	No ethics approval is required as the systematic review will use only published data already in the public domair	۱.
9 10	306	Findings will be disseminated through publication in a peer reviewed journal.	
11	307		
12 13	308	Author's contributions	
14 15	309	JP, GDH, BMK and RM conceived this study. JP developed the study protocol with the help of BMK and RM. JP w	ill
15 16	310	implement the review under the supervision of RM. JP and HH will perform the study search, screening, and	
17 18	311	extraction of data under the guidance of RM. LA and BMK will provide methodological expertise for this review.	SS,
19	312	LG, WS, MS and GDH will provide content expertise for this review and all authors will provide comments on the	2
20 21	313	final manuscript before publication. JP will be the guarantor of this review.	
22	314		
23 24	315	Funding	
25	316	This research received no specific grant from any funding agency in the public, commercial or not-for-profit	
26 27	317	sectors. The Vaccines for Africa Initiative (VACFA) has funded the costs associated with the research and	
28	318	dissemination of the results, including publications.	
29 30	319		
31	320	Competing interests	
32 33	321	None declared.	
34 35	322		
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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 point
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 point

#### Appendix 2

#### **PRISMA-P** Checklist

Section and topic	Item No	Checklist item	(Pag No.#
ADMINISTRATIVE INF	ORMATIO	N	
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&
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/#
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//
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 $\tau$ )	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

# **BMJ Open**

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2019-029819.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Jul-2019
Complete List of Authors:	Patterson, Jenna; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Hussey, Hannah; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Abdullahi, Leila; Save the Children International, Research, Evaluation, Analysis, Learning and Monitoring (REALM) Silal, Sheetal; University of Cape Town, Department of Statistical Sciences; University of Oxford, Nuffield Department of Medicine Goddard, Liz; University of Cape Town, Department of Paediatrics, Red Cross War Memorial Children's Hospital Setshedi, Mashiko; University of Cape Town, Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital Spearman, Wendy ; University of Cape Town, Department of Medicine, Division of Hepatology, Groote Schuur Hospital Hussey, Gregory; University of Cape Town, School of Public Health & Family Medicine, Vaccines For Africa Initiative; University of Cape Town, Institute of Infectious Disease and Molecular Medicine Kagina, Benjamin; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Muloiwa, Rudzani; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Muloiwa, Rudzani; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Muloiwa, Rudzani; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative Muloiwa, Rudzani; University of Cape Town, School of Public Health & Family Medicine, Vaccines for Africa Initiative; University of Cape Town, Department of Paediatrics, Groote Schuur Hospital
<b>Primary Subject Heading</b> :	Epidemiology
Secondary Subject Heading:	Gastroenterology and hepatology, Infectious diseases
Keywords:	Epidemiology < INFECTIOUS DISEASES, acute liver failure, VIROLOGY

# SCHOLARONE<sup>™</sup> Manuscripts

1 2		
2 3 4	1	PROTOCOL
5	2	
7 8	3	The Global Epidemiology of Viral-Induced Acute Liver Failure: A Systematic Review Protocol
9 10	4 5	Jenna Patterson <sup>1,2</sup> , Hannah Hussey <sup>1,2</sup> , Leila Abdullahi <sup>2.4</sup> , Sheetal Silal <sup>5</sup> , Liz Goddard <sup>6</sup> , Mashiko
11	6	Setshedi <sup>7</sup> , Wendy Spearman <sup>7</sup> , Gregory D. Hussey <sup>1,8</sup> , Benjamin M. Kagina <sup>1,2</sup> and Rudzani
12 13	7	Muloiwa <sup>1,6</sup>
14 15		Muloiwa-/-
15 16	8	
17 18	9 10	
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	18	Town, South Africa
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49 50 51 52 53 54	29	
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	32	Corresponding author's postal address: Vaccines for Africa Initiative, Room N2.09A, Werner Beit North, Health
55 56	33	Sciences Campus, Anzio Road, Observatory, 7925
57 58		1
58 59		Patterson, J et al.
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2 3	34	ABSTRACT
4 5	35	Introduction: The burden of viral-induced ALF around the world still remains unclear, with little to no data
6	36	collected regarding the disease incidence in general and synthesised data on the relative contribution of different
7 8	37	viruses to the aetiology of ALF is missing in the field. The aim of this review is to estimate the burden (prevalence,
9	38	incidence, mortality, hospitalization) of ALF following infection HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV,
10 11	39	parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs. Establishing the common aetiologies of viral-
12	40	induced acute liver failure, which vary geographically, is important so that: a) treatment can be initiated quickly, b)
13 14	41	contraindications to liver transplant can be identified, c) prognoses can be determined more accurately, and most
15 16	42	importantly, d) vaccination against viral ALF aetiologies can be prioritised especially in under-resourced regions
17	43	with public health risks associated with the relevant attributable diseases.
18 19	44	
20	45	Methods and analysis: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science databases will be searched
21 22	46	for relevant literature published and grey literature from 2009 up to 2019. Published cross-sectional and cohort
23	47	studies will be eligible for inclusion in this review. Qualifying studies will be formally assessed for quality and risk of
24 25	48	bias using a standardised scoring tool. Following standardised data extraction, meta-analyses will be carried out
26	49	using STATA. Depending on characteristics of included studies, subgroup analyses and meta-regression analyses
27 28	50	will be performed. This review will be reported according to Preferred Reporting Items for Systematic reviews and
29	51	Meta-Analyses (PRISMA) guidelines.
30 31	52	
32 33	53	Ethics and dissemination: No ethics approval is required as the systematic review will use only published data
33 34	54	already in the public domain. Findings will be disseminated through publication in a peer reviewed journal.
35 36	55	
37	56	Registration: This protocol has been registered with the International Prospective Register of Systematic Reviews
38 39	57	(PROSPERO), registration number CRD42018110309.
40	58	
41 42	59	Key words: global, epidemiology, acute liver failure
43	60	
44 45	61	Strengths and limitations of study:
46	62	Comprehensive and exhaustive search for relevant studies from several databases
47 48	63	Comprehensive diagnostic inclusion criteria for acute liver failure cases according to international
49 50	64	guidelines
50 51	65	• Paucity of data may lead to meta-analysis and/or meta-regression analysis not being possible for all global
52 53	66	regions
54	67	• Diversity of viruses attributable to ALF cases may lead to low statistical power in meta-analysis
55 56	68	
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3 4	69	MAIN TEXT
5	70	INTRODUCTION
6 7	71	Acute liver failure (ALF) refers to a rare syndrome characterised by an acute liver injury resulting in encephalopathy
8	72	(altered mentation) and coagulopathy (International Normalised Ratio (INR) >1.5 ) in individuals without known
9 10	73	pre-existing liver disease and with an illness of <26 weeks duration (1). The syndrome was originally defined as
11	74	fulminant liver failure or fulminant hepatic failure in 1970 but was re-defined as ALF in the early 1990s when the
12 13	75	understanding of the multiple disease aetiologies, frequency of complications and prognosis of the condition
14	76	further developed (2). Further sub-classifications of ALF include hyperacute, acute and subacute depending on the
15 16	77	time in weeks from the development of jaundice to the development of hepatic encephalopathy (3).
17	78	
18 19	79	The pathogenesis of ALF includes both direct and immune-mediated liver injury triggered by the disease aetiology
20	80	(4). The aetiology of ALF determines the clinical course and progression of the disease and well as the need for
21 22	81	specific therapy (5). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver
23	82	diseases (acute fatty liver of pregnancy, HELLP syndrome, preeclampsia), vascular causes (Budd-Chiari syndrome,
24 25	83	ischaemic hepatitis) and malignancy (lymphoma, haemophagocytic lymphohistiocytosis). Wilsons disease,
26	84	vertically-acquired hepatitis B and autoimmune hepatitis are included despite being chronic liver diseases if the
27 28	85	diagnosis is made within 26 weeks (6).
29	86	
30 31	87	Acute viral hepatitis (particularly acute hepatitis A and acute E) has been identified as the most common cause of
32	88	ALF among all ages in Asia and Africa and the most common causes of ALF in children in Asia and South America (2,
33 34	89	4). The incidence of virally induced ALF has substantially declined in Europe, with only 19% of all ALF cases now
35	90	related to viral infection (2). Vaccination has led to a significant drop in the incidence of acute hepatitis B induced
36 37	91	ALF, with fewer than 4% of ALF cases now attributable to hepatitis B infection in Europe (2). Since the introduction
38	92	of a universal one-dose hepatitis A vaccination program in Argentina, the number of acute hepatitis A induced ALF
39 40	93	cases has decreased from 54.6% to 27.7% (7).
41		
42 43	94	The most common causes of death in patients with ALF are cerebral oedema and multi-organ system failure (4).
44	95	Mortality rates associated with ALF vary between 60% and 80%, depending on the disease aetiology as well as a
45 46	96	patient's access to care (8, 9). Liver transplantation plays a central role in the management of ALF and remains the
47	97	only definitive treatment for patients who fail to demonstrate spontaneous recovery (1). It remains difficult to
48 49	98	predict which patients with ALF will require transplantation and models such as the "Model for End-stage Liver
50	99	Disease" (MELD) have not improved the accuracy of these predictions (1). The King's College Criteria for
51 52	100	emergency liver transplantation remains the most clinically useful, with a sensitivity of 68%-69% and a specificity
53	101	of 82%-92% (10). Management of ALF cases accounts for 5-12% of all liver transplant activity in the United States
54 55	102	and Europe (11). A large proportion of patients with ALF in both high and low resource settings, however, are
56		
57 58		3

deemed to have contraindications to transplantation or deteriorate beyond transplantation before a donor liver is

1 2 3

4	105	decined to have contraindications to transplantation of deteriorate beyond transplantation before a donor inversi
4 5 6	104	allocated (5, 11, 12).
7 8	105	The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding
9	106	the disease incidence in general (2). Epidemiological estimates around ALF are based purely on data from
10 11	107	transplant units and the medical management of the condition remains poorly defined (1, 2). Establishing the
12	108	common aetiologies of viral-induced ALF, which vary geographically, is important so that: a) treatment can be
13 14	109	initiated quickly, b) contraindications to liver transplant can be identified, c) prognoses can be determined more
15	110	accurately, and most important, d) vaccination against viral ALF aetiologies can be prioritised especially in under-
16 17	111	resourced regions with public health risks associated with the relevant attributable diseases.
18	112	
19 20	113	To the best of our knowledge, no extensive systematic review of the global epidemiology of viral-induced ALF has
21	114	previously been conducted. Furthermore, synthesised data on the relative contribution of different viruses to the
22 23	115	aetiology of ALF is missing in the field. Hepatitis A is a major cause of ALF and the epidemiology of the disease is
24	116	changing on a global scale. For example, it has been reported in many low and middle-income countries, that the
25 26	117	epidemiology hepatitis A is transitioning from high to intermediate endemicity and this transition is associated
27 20	118	with an increasing incidence of acute hepatitis A (13-15). This review aims to describe the global epidemiology of
28 29	119	viral-induced ALF.
30 31	120	
32	121	Aim
33 34	122	To estimate the burden (prevalence, incidence, mortality, hospitalization) of ALF following infection HAV, HBV,
35	123	HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 and/or HAdVs.
36 37	124	
38	125	METHODS
39 40	126	Patient and Public Involvement
41	127	This research question was developed as part of an ongoing project by the research team that aims to generate
42 43	128	evidence to facilitate evidence-based decision making of introducing routine hepatitis A vaccination in South
44	129	Africa. The findings of this review will contribute to the knowledge base that aims to enhance global vaccination
45 46	130	strategies against viral-associated ALF. As this is a systematic review, no patient involvement will be required;
47	131	however, it is hoped that the findings of this review will help to highlight the burden that acute liver failure places
48 49	132	on populations without routine hepatitis A vaccination. Findings will be disseminated through publication in a peer
50	133	reviewed journal and included in a technical policy dossier distributed to the National Advisory Group on
51 52	134	Immunisation in South Africa.
53	135	
54 55	136	
56 57		
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1		
3	137	Criteria for considering studies for this review
4 5	138	Types of studies
6	139	Only published cross-sectional, surveillance and cohort studies will be eligible for inclusion in this review.
7 8	140	
9 10	141	Types of participants
10	142	Patients of any age with any of the following viral infections: hepatitis A virus (HAV), hepatitis B virus (HBV),
12 13	143	hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes simplex
13 14	144	virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza
15 16	145	viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV), coxsackievirus
17	146	(CA16) and adenovirus (HAdVs).
18 19	147	
20	148	Case definition
21 22	149	Included studies must have a clearly stated case definition of viral-induced acute liver failure. Cases must be
23	150	confirmed by both clinical and laboratory diagnostic methods.
24 25	151	Clinical diagnosis of ALF will be defined as follows for children and adults presenting with an acute liver
26	152	injury:
27 28	153	• Children – The absence of known, chronic liver disease with liver-based coagulopathy not
29	154	responsive to parenteral vitamin K and an international normalised ratio (INR) ≥ 1.5 in the
30 31	155	presence of clinical evidence of encephalopathy or INR of ≥ 2.0 without clinical signs of
32	156	encephalopathy (16)
33 34	157	• Adults – Liver-based coagulopathy (INR $\geq$ 1.5) and any grade of hepatic encephalopathy (HE) as
35	158	defined by the West Haven criteria within 26 weeks after the onset of symptoms but with no
36 37	159	evidence of chronic liver disease, including cirrhosis (1, 17)
38	160	• Serological, molecular or culture laboratory confirmation of infection with HAV, HBV, HCV, HDV, HEV,
39 40	161	EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 or HAdVs.
41	162	
42 43	163	Exclusion criteria
44	164	Studies will be excluded from this review if they do not report any of the primary outcomes listed or do not match
45 46	165	the clearly stated case definition of viral-induced acute liver failure given for this review.
47	166	
48 49	167	
50	168	
51 52	169	
53 54	170	
54 55	171	
56 57		_
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50		

2				
3 4	172			
5	173	Outcom	es	
5 7	174	For ALF	following	infection with HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV,
8	175	HVV-6, (	CMV, CA16	5 and/or HAdVs:
9 10	176	•	Prevalenc	ce and incidence of ALF
11	177	•	Mortality	rate following ALF
12 13	178	•	Prevalence	ce and incidence of requirement for liver transplant
14	179	•	Mean ho	spital stay for patients with ALF
5 6	180			
7	181	Search I	Methods	
8 9	182	The liter	ature sear	rch strategy will use both text words and medical subject heading (MeSH) terms (all fields). It will
20	183	include	the follow	ing terms: epidemiology, prevalence, incidence, burden, mortality, morbidity, fulminant hepatic
21 22	184	failure, f	ulminant	liver failure, acute hepatic failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus
23	185	(HBV), h	epatitis C	virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), epstein-barr virus (EBV), herpes
24 25	186	simplex	virus-1 (H	SV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human
26	187	parainflu	uenza viru	ses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HVV-6), cytomegalovirus (CMV) and
27 28	188	coxsacki	e virus. Th	nese terms will be adapted for use in each defined database and combined with relevant filters
29 30	189	for time	period of	studies eligible for inclusion in the review. <b>Table 1</b> shows an example search strategy for use in
30 31	190	PubMed	l. Each ada	apted search strategy for use in the outlined databases will be piloted by JP and HH to ensure the
32 33	191	outputs	retrieved	are relevant to the review objectives.
34	192			
35 36	193	The follo	owing elec	tronic databases will be searched from 2009 up to 2019 for relevant published literature:
37	194	EBSCOh	ost, PubM	ed, ScienceDirect, Scopus and Web of Science. The starting date of 2009 was chosen as Bernal et
38 39	195	al. 2010	complete	d searched Medline with the terms "acute liver failure" and "fulminant hepatic failure" between
40	196	1997 an	d 2009, wl	hich provided a review of the most relevant publications to practice. No language restriction will
41 42	197	be place	s on the s	earch for studies (8).
43	198			
44 45		Table 1 Query	L: Search stra	ategy for use in PUBMED
46		#1	All fields	epidemiology OR prevalence OR incidence OR burden OR mortality OR morbidity
47 48				
49		#2	All fields	fulminant OR acute
50 51		#3	All fields	hepatic failure OR liver failure
52 53 54		#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

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	#5	All fields	humans				
	#6	N/A	#1 AND #2 AND #3 AND #4 AND #5				
	Selecti	ion of studie	1 25	]			
	All ele	ctronic data	base outputs will be imported to Rayyan Software for screening and selection. The first and				
	second	d author will	independently screen 100% titles and abstracts for inclusion of potentially eligible trials sour	ced			
	databa	ase searches	. Titles and abstracts in non-English languages will be translated into English using Google				
	Transla	ate. HH will	collect full-text trials reports/publications of potentially eligible studies and then HH and JP w	ʻill			
	indepe	endently scr	een 100% of full-text articles for inclusion. Where disagreement may occur between the two				
	author	rs, the last a	uthor (RM) will be consulted. We will record the selection process with reasons for exclusion				
	using a	a PRISMA flo	w diagram.				
	Data e	extraction a	nd dealing with missing data				
	Two a	uthors (JP ar	nd HH) will independently extract data from the included studies on a standardised, pre-desig	ned			
	extrac	tion form. Ir	the event of any disagreement between the two authors, a third author (RM) will be consult	ed.			
	In the	case where	non-English studies are selected for inclusion in the review, GoogleTranslate will be used to				
	allow f	for data extr	action (18). In the event that data are missing, we will contact the investigators or study				
	sponse	sponsors to obtain the missing data. In the event of no reply within one month, we will exclude the study from the					
	outcor	ne respectiv	re to the missing data. Studies awaiting missing data requests will be marked as "awaiting				
	classifi	cation" in th	ne table of included studies.				
	The fo	llowing info	rmation will be extracted from the included studies:				
	• St	udy charact	eristics: year of publication, study design, sample size and objectives of study				
	• St	udy populat	ion: country, WHO region, country income level, hepatitis A vaccination program (yes or no)				
	• Ca	ase definitio	n: clinical case definition and laboratory confirmation methods and the type of virus or viruse	S			
	in	dicated as t	ne causative agent for the condition				
	• Ca	ase characte	ristics: age, gender, hepatitis A vaccination status, country of residence and immune suppress	sive			
	СС	onditions (e.	g. HIV, cancer and diabetes, immunosuppression, chemotherapy)				
4							
5	Data n	nanagemen	t				
6	Data n	nanagement	will be the responsibility of the first author (JP) in consultation with SS, BMK and RM. An				
	electro	onic parent f	older with the name of this study will be created. Subfolders will also be created to keep the				
8	details	of different	tasks completed such as all records retrieved, records included and excluded, risk of bias				
)	assess	ment result	s, analyses and full systematic review manuscript drafts. Two back-ups of the parent folder wi	ill			
)	be cre	ated and sto	ored on a memory stick and a hard drive.				
				7			
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1 2			
3	232		
4 5	233		
6	234	Risk of bias assessment of included studies	
7 8	235	Two review authors will independently assess the risk of bias for each included study using the Cochrane domain-	
9 10	236	based evaluation for experimental studies and the 2012 Hoy et al., tool for observational studies (19, 20). In case	
10	237	of disagreement, a third author will be consulted to resolve the inconsistencies. A version of Hoy et al., tool is	
12 13	238	shown in Appendix 1. For included experimental study, we will report bias assessments in the form of a risk of bias	
14	239	graphs created in RevMan (21). For included observational studies, we report risk of bias together with a	
15 16	240	descriptive summary of the information that influenced our judgment in a risk of bias table. We will judge	
17	241	observational studies as having 'low risk', 'unclear risk' or 'high risk' of bias.	
18 19	242		
20	243	Assessment of heterogeneity	
	244	We will use forest plots to assess the presence of statistical heterogeneity. We will assess heterogeneity by	
23	245	calculating Chi <sup>2</sup> (threshold P > 0.1) and I <sup>2</sup> statistics (threshold I <sup>2</sup> > 40%). The values of I <sup>2</sup> will be categorised for	
	246	heterogeneity as follow: "not important" (0 to 40%), "moderate" (41 to 60%) and "considerable" (61 to 80%) and	
26 27 28 29	247	"substantial" (81 to 100%). Where "not important" or "moderate" heterogeneity exists between studies (I² $\leq$	
	248	40%), the outcomes will be pooled in a meta-analysis and reported using forest plots. Where "considerable" or	
	249	"substantial" heterogeneity exists between studies (I <sup>2</sup> > 40%), the outcomes will be reported in narrative form and	
30 31	250	displayed using forest plots.	
29 30 31 32 33 34 35 36 37	251		
	252	Assessment of reporting biases	
	253	A funnel plot will be constructed to assess the risk of publication bias included in the meta-analysis with over 10	
	254	studies of varying sizes. The funnel plot will be examined for asymmetry visually and statistically using the Egger	
38 39	255	test (22).	
21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	256		
	257	Data synthesis	
43	258	Proportions as percentages will be used to represent measures of frequency prioritised by the primary and	
	259	secondary outcomes of the review. Included studies for each analysis will be assessed for heterogeneity using the	
46	260	I <sup>2</sup> statistic. Where sufficient homogeneity exists ( $l^2 <$ 50%) between studies, data will be pooled in a meta-	
	261	analysis. Prevalence data from individual studies will be pooled together using random-effects meta-analysis. The	
49	262	pooled estimates will be calculated after a Freeman-Tukey double arcsine transformation and presented in forest	
	263	plots. For incidence data, meta-analysis models will be applied using the log incidence rates and the corresponding	
52	264	standard errors. The pooled data will be reverse transformed and presented in forest plots. For rare events,	
	265	incidences will be pooled using Poisson based mixed-effects models. Both outcome measures will be reported with	
	266	uncertainty expressed using 95% confidence intervals (CI). Where data are too heterogeneous ( $I^2 \geq 50$ %),	
		8	
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1 2			
2 3	267	outcome estimates will be reported narratively. STATA software V.14 (STATA Corporation, College Stations, Texas	,
4 5	268	USA) will be used to compute all statistical analyses in this review.	
6	269		
7 8	270	Subgroup analysis	
9	271	Where sufficient data exists, subgroup analyses will be conducted according to the groupings below. Meta-	
10 11	272	regression analyses will be conducted for all sub-groups where there are $\geq$ 10 studies for inclusion in the analysis	s.
12 13	273	• Study design	
14	274	• 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,	
15 16	275	31 to 40 years old, 41 to 50 years old, 51 to 60 years old, $> 60$ years old)	
17 18	276 277	• These age groups have been used as individuals > 60 years old are considered "elderly" in the acute liver failure literature reviewed	
19 20	278	HIV status (not exposed/not infected, exposed/not-infected, infected)	
21	279	• Country	
22 23	280	WHO region	
24 25	281	Countries with and without routine hepatitis A vaccination programs	
26	282	Length of routine hepatitis A vaccination in a country	
27 28 29 30 31 32 33 34	283		
	284	Sensitivity analysis	
	285	Inclusion/exclusion analyses will be performed in order to assess the potential impact of risk of bias on the	
	286	robustness of outcome estimates. We will conduct analyses to provide three estimates of intervention effects in	
	287	respect to bias; outcome estimates with inclusion of only studies at low risk of bias, outcome estimates with	
35 36	288	inclusion of only studies at high risk of bias and outcome estimates with inclusion of all studies. Where	
37	289	inconsistencies exist between outcome estimates with inclusion of only studies at low risk of bias and the outcom	e
38 39	290	estimates of only studies at high risk or all included studies, these inconsistencies will be reported. Further,	
40	291	outcome estimates of studies at low and high risk will be interpreted separately in the review.	
41 42	292		
43 44	293	Reporting of the review	
44 45	294	This review will be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses	
46 47	295	(PRISMA) guidelines (Appendix 2). The study selection process will be summarised using a PRISMA flow diagram.	
48	296	Tables will be used to summarise both qualitative and quantitative data from individual studies included in the	
49 50	297	review. Quantitative data from the review will be presented using narrative descriptions, forest plots and graphs	
51	298	where relevant.	
52 53	299		
54	300	Systematic Review Registration	
55 56			
57 58			9
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1 2

3	301	This protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO),	
4 5	302	registration number (CRD42018110309).	
6 7	303		
8	304		
9 10	305	Ethics and dissemination	
11	306	No ethics approval is required as the systematic review will use only published data already in the public domain.	
12 13	307	Findings will be disseminated through publication in a peer reviewed journal.	
14 15	308		
16	309	Author's contributions	
17 18	310	JP, GDH, BMK and RM conceived this study. JP developed the study protocol with the help of BMK and RM. JP wil	I
19	311	implement the review under the supervision of RM. JP and HH will perform the study search, screening, and	
20 21	312	extraction of data under the guidance of RM. LA and BMK will provide methodological expertise for this review. S	S,
22	313	LG, WS, MS and GDH will provide content expertise for this review and all authors will provide comments on the	
23 24	314	final manuscript before publication. JP will be the guarantor of this review.	
25	315		
26 27	316	Funding	
28	317	This research received no specific grant from any funding agency in the public, commercial or not-for-profit	
29 30	318	sectors. The Vaccines for Africa Initiative (VACFA) has funded the costs associated with the research and	
31 22	319	dissemination of the results, including publications.	
32 33	320		
34 35	321	Competing interests	
36	322	None declared.	
37 38	323		
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#### Appendix 1

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

External validity		
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 point	
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 point	

#### Appendix 2

#### **PRISMA-P** Checklist

Section and topic	Item No	Checklist item	(Pag No.#
ADMINISTRATIVE INF	ORMATIO	N	
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&
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/#
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//
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 $\tau$ )	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