

# BMJ Open The global epidemiology of viral-induced acute liver failure: a systematic review protocol

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## ABSTRACT

**Introduction** The burden of viral-induced acute liver failure (ALF) around the world still remains unclear, with little to no data collected regarding the disease incidence in general and synthesised data on the relative contribution of different viruses to the aetiology of ALF is missing in the field. The aim of this review is to estimate the burden (prevalence, incidence, mortality, hospitalisation) of ALF following infection *HAV*, *HBV*, *HCV*, *HDV*, *HEV*, *EBV*, *HSV1*, *HSV2*, *VZV*, *parvo-virus B19*, *HPIVs*, *YFV*, *HVV-6*, *CMV*, *CA16* and/or *HAdVs*. Establishing the common aetiologies of viral-induced ALF, which vary geographically, is important so that: (1) treatment can be initiated quickly, (2) contraindications to liver transplant can be identified, (3) prognoses can be determined more accurately, and most importantly, (4) vaccination against viral ALF aetiologies can be prioritised especially in under-resourced regions with public health risks associated with the relevant attributable diseases.

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

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

**PROSPERO registration number** CRD42018110309

## INTRODUCTION

Acute liver failure (ALF) refers to a rare syndrome characterised by an acute liver injury resulting in encephalopathy (altered mentation) and coagulopathy (International Normalised Ratio (INR) >1.5) in individuals without known pre-existing liver disease and with an illness of <26 weeks' duration.<sup>1</sup> The

## Strengths and limitations of this study

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

syndrome was originally defined as fulminant liver failure or fulminant hepatic failure in 1970 but was redefined as ALF in the early 1990s when the understanding of the multiple disease aetiologies, frequency of complications and prognosis of the condition further developed.<sup>2</sup> Further subclassifications of ALF include hyperacute, acute and subacute depending on the time in weeks from the development of jaundice to the development of hepatic encephalopathy (HE).<sup>3</sup>

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



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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.<sup>2,4</sup> The incidence of virally induced ALF has substantially declined in Europe, with only 19% of all ALF cases now related to viral infection.<sup>2</sup> 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.<sup>2</sup> Since the introduction of a universal one-dose hepatitis A vaccination programme in Argentina, the number of acute hepatitis A-induced ALF cases has decreased from 54.6% to 27.7%.<sup>7</sup>

The most common causes of death in patients with ALF are cerebral oedema and multiorgan system failure.<sup>4</sup> Mortality rates associated with ALF vary between 60% and 80%, depending on the disease aetiology as well as a patient's access to care.<sup>8,9</sup> 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.<sup>1</sup> It remains difficult to predict which patients with ALF will require transplantation and models such as the 'Model for End-stage Liver Disease' have not improved the accuracy of these predictions.<sup>1</sup> The King's College Criteria for emergency liver transplantation remain the most clinically useful, with a sensitivity of 68%–69% and a specificity of 82%–92%.<sup>10</sup> Management of ALF cases accounts for 5%–12% of all liver transplant activity in the USA and Europe.<sup>11</sup> A large proportion of patients with ALF in both high/low-resource settings, however, are deemed to have contraindications to transplantation or deteriorate beyond transplantation before a donor liver is allocated.<sup>5,11,12</sup>

The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence in general.<sup>2</sup> Epidemiological estimates around ALF are based purely on data from transplant units and the medical management of the condition remains poorly defined.<sup>1,2</sup> Establishing the common aetiologies of viral-induced ALF, which vary geographically, is important so that: (1) treatment can be initiated quickly, (2) contraindications to liver transplant can be identified, (3) prognoses can be determined more accurately, and most important, (4) vaccination against viral ALF aetiologies can be prioritised especially in under-resourced regions with public health risks associated with the relevant attributable diseases.

To the best of our knowledge, no extensive systematic review of the global epidemiology of viral-induced ALF has previously been conducted. Furthermore, synthesised data on the relative contribution of different viruses to the aetiology of ALF are 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/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.<sup>13–15</sup> This review aims to describe the global epidemiology of viral-induced ALF.

## Aim

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

## METHODS

### Patient and public involvement

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

### Criteria for considering studies for this review

#### Types of studies

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

#### Types of participants

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

#### Case definition

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

1. 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 INR  $\geq 1.5$  in the presence of clinical evidence of encephalopathy or INR of  $\geq 2.0$  without clinical signs of encephalopathy.<sup>16</sup>

Adults—liver-based coagulopathy (INR  $\geq 1.5$ ) and any grade of HE as defined by the West Haven criteria with-

in 26 weeks after the onset of symptoms but with no evidence of chronic liver disease, including cirrhosis.<sup>117</sup>

2. Serological, molecular or culture laboratory confirmation of infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HHV-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 ALF given for this review.

### Outcomes

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

1. Prevalence and incidence of ALF.
2. Mortality rate following ALF.
3. Prevalence and incidence of requirement for liver transplant.
4. Mean hospital stay for patients with ALF.

### Search methods

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

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

### Selection of studies

All electronic database outputs will be imported to Rayyan Software for screening and selection. The first and second author will independently screen 100% titles and abstracts for inclusion of potentially eligible

**Table 1** Search strategy for use in PubMed

Query	Fields	Search term
#1	All fields	epidemiology OR prevalence OR incidence OR burden OR mortality OR morbidity
#2	All fields	fulminant OR acute
#3	All fields	hepatic failure OR liver failure
#4	All fields	hepatitis a virus OR HAV OR hepatitis b virus OR HBV OR hepatitis c virus OR HCV OR HCV OR hepatitis d virus OR HDV OR hepatitis e virus OR HEV OR epstein-barr virus OR EBV OR herpes simplex virus-1 OR HSV1 OR herpes simplex virus-2 OR HSV2 OR varicella-zoster virus OR VZV OR parvovirus b19 OR human parainfluenza viruses OR yellow fever virus OR YFV OR human herpesvirus 6 OR HHV-6 OR cytomegalovirus OR CMV OR adenovirus OR HAdVs
#5	All fields	humans
#6	N/A	#1 AND #2 AND #3 AND #4 AND #5

trials sourced database searches. Titles and abstracts in non-English languages will be translated into English using Google Translate. HSH will collect full-text trials reports/publications of potentially eligible studies and then HSH and JP will independently screen 100% of full-text articles for inclusion. Where disagreement may occur between the two authors, the last author (RM) will be consulted. We will record the selection process with reasons for exclusion using a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.

### Data extraction and dealing with missing data

Two authors (JP and HSH) 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.<sup>18</sup> 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 1 month, we will exclude the study from the outcome respective to the missing data. Studies awaiting missing data requests will be marked as 'awaiting classification' in the table of included studies.

The following information will be extracted from the included studies:

1. Study characteristics: year of publication, study design, sample size and objectives of study.

2. Study population: country, WHO region, country income level, hepatitis A vaccination programme (yes or no)
3. Case definition: clinical case definition and laboratory confirmation methods and the type of virus or viruses indicated as the causative agent for the condition
4. Case characteristics: age, gender, hepatitis A vaccination status, country of residence and immune suppressive conditions (eg, HIV, cancer and diabetes, immunosuppression, chemotherapy)

### Data management

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

### Risk of bias assessment of included studies

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

### Assessment of heterogeneity

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

### Assessment of reporting biases

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

### Data synthesis

Proportions as percentages will be used to represent measures of frequency prioritised by the primary and secondary outcomes of the review. Included studies for each analysis will be assessed for heterogeneity using the  $I^2$  statistic. Where sufficient homogeneity exists ( $I^2 < 50\%$ ) between studies, data will be pooled in a meta-analysis. Prevalence data from individual studies will be pooled together using random-effects meta-analysis. The pooled estimates will be calculated after a Freeman-Tukey double arcsine transformation and presented in forest plots. For incidence data, meta-analysis models will be applied using the log incidence rates and the corresponding SEs. The pooled data will be reverse transformed and presented in forest plots. For rare events, incidences will be pooled using Poisson based mixed-effects models. Both outcome measures will be reported with uncertainty expressed using 95% CI. Where data are too heterogeneous ( $I^2 \geq 50\%$ ), outcome estimates will be reported narratively. STATA software V.14 will be used to compute all statistical analyses in this review.

### Subgroup analysis

Where sufficient data exist, subgroup analyses will be conducted according to the groupings below. Meta-regression analyses will be conducted for all subgroups where there are  $\geq 10$  studies for inclusion in the analysis.

1. Study design.
2. Age-groups (1–5, 6–10, 11–15, 16–20, 21–30, 31–40, 41–50, 51–60, >60 years old). Age groups have been used as individuals 60 years old are considered selected as individuals 60 years old are considered 'elderly' in the ALF literature reviewed.
3. HIV status (not exposed/not infected, exposed/not-infected, infected).
4. Country.
5. WHO region.
6. Countries with and without routine hepatitis A vaccination programmes.
7. Length of routine hepatitis A vaccination in a country.

### Sensitivity analysis

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

### Reporting of the review

This review will be reported according to PRISMA guidelines (online supplementary appendix 2). The study

selection process will be summarised using a PRISMA flow diagram. Tables will be used to summarise both qualitative and quantitative data from individual studies included in the review. Quantitative data from the review will be presented using narrative descriptions, forest plots and graphs where relevant.

### Systematic review registration

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

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**Contributors** 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 HSH will perform the study search, screening and extraction of data under the guidance of RM. LHA and BK will provide methodological expertise for this review. SS, LG, WS, MS and GDH will provide content expertise for this review and all authors will provide comments on the final manuscript before publication. JP will be the guarantor of this review.

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