BMJ Open

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

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-037473 |
| Article Type: | Original research |
| Date Submitted by the Author: | 07-Feb-2020 |
| Complete List of Authors: | Patterson, Jenna; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Hussey, Hannah; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health & Family Medicine<br>Silal, Sheetal; University of Cape Town, Department of Statistical Sciences; University of Oxford, Nuffield Department of Medicine<br>Goddard, Liz; University of Cape Town, Department of Paediatrics, Red Cross War Memorial Children's Hospital<br>Setshedi, Mashiko; University of Cape Town, Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital<br>Spearman, Wendy ; University of Cape Town, Department of Medicine, Division of Hepatology, Groote Schuur Hospital<br>Hussey, Gregory; University of Cape Town Faculty of Health Sciences, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Kagina, Benjamin; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Muloiwa, Rudzani; University of Cape Town, 5Department of Pediatrics & Child Health, Red Cross War Memorial Children's Hospital; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiaitve, School of Public Health and Family Medicine |
| Keywords: | Epidemiology < INFECTIOUS DISEASES, Hepatology < INTERNAL MEDICINE, VIROLOGY |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

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

Jenna Patterson[1,2], Hannah Sophia Hussey[1,2], Sheetal Silal[3,4], Liz Goddard[5], Mashiko Setshedi[6], C. Wendy Spearman[7], Gregory D. Hussey[1,8] Benjamin M. Kagina[1,2] and Rudzani Muloiwa[1,5]

[1]Vaccines for Africa Initiative, University of Cape Town, South Africa

[2]School of Public Health & Family Medicine, University of Cape Town, South Africa

[3]Modelling and Simulation Hub, Africa, Department of Statistical Sciences, Faculty of Science, University of Cape Town, South Africa

[4]Nuffield Department of Medicine, Oxford University, Oxford, United Kingdom

[5]Department of Pediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town

[6]Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital, University of Cape Town, South Africa

[7]Division of Hepatology, Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital, South Africa

[8]Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa

[5]Department of Pediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town

*Corresponding author*: Jenna Patterson

*Corresponding author's ORCID iD:* 0000-0002-3927-037X

*Corresponding author's email address*: pttjen005@myuct.ac.za

*Corresponding author's postal address:* Vaccines for Africa Initiative, Room N2.09A, Werner Beit North, Health Sciences Campus, Anzio Road, Observatory, 7925

*H.S. Hussey email address:* hshussey@gmail.com

*S. Silal email address:* sheetal.silal@uct.ac.za

*E. Goddard email address:* liz.goddard@uct.ac.za

*M. Setshedi email address:* mashiko.setshedi@uct.ac.za

*W. Spearman email address:* wendy.spearman@uct.ac.za

*G.D. Hussey email address:* gregory.hussey@uct.ac.za

*B.M. Kagina email address:* benjamin.kagina@uct.ac.za

*R. Muloiwa email address:* rudzani.muloiwa@uct.ac.za

## REQUIRED STATEMENTS

**Funding statement**

This project was not supported by any funding source.

**Conflict of interest disclosure**

All authors have no conflicts of interest to declare.

**Ethics approval statement**

This study did not require ethics approval as it uses publicly available, published data.

**Patient consent statement**

This study did not require consent from patients as it uses no individual data.

**Permission to reproduce material from other sources**

This study has cited all references which are published and publicly available.

## ABBREVIATIONS

- Acute liver failure (ALF)
- 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)
- Human parainfluenza viruses (HPIVs)
- Yellow fever virus (YFV)
- Human herpesvirus 6 (HHV-6)
- Cytomegalovirus (CMV)
- Coxsackievirus (CA16)
- Adenovirus (HAdVs)
- Medical Subject Headings (MESH)
- Low- and middle- income countries (LMICs)

## ABSTRACT

**Objectives:** The etiology and burden of viral-induced acute liver failure (ALF) remains unclear, globally (1). It is important to understand the epidemiology of viral-induced ALF to plan for clinical case management and case prevention.

**Participants:** This systematic review was conducted to synthesize data on the relative contribution of different viruses to the etiology of viral-induced ALF in attempt to compile evidence that is currently missing in the field. Five electronic databases were searched for relevant literature from 2009 to 2019. Twenty-five eligible studies were included in the results of this review.

**Results:** This systematic review estimated the burden of acute liver failure following infection with HBV, HAV, HBV, HCV, HEV, HSV/HHV, CMV, EBV, and parvo-virus B19. Data were largely missing for ALF following infection with VZV, HPIVs, YFV, CA16 and/or HAdVs. The prevalence of HAV-induced ALF was markedly lower in countries with routine HAV immunization vs no routine HAV immunization. Hepatitis E virus was the most common etiological cause of viral-induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which appear to increase with poor economic status of the studied countries.

**Conclusions:** Immunization against HAV and HBV should be prioritized in LMICs to prevent high viral-induced ALF mortality rates, especially in settings where resources for managing acute liver failure are lacking. The expanded use of HEV immunization should be explored as HEV was the most common cause of ALF.

**Registration:** PROSPERO registration number CRD42017079730


**Strengths and limitations**

- Findings are limited by lack of data for some of the viral etiologies of ALF including for VZV, HPIVs, YFV, CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced ALF
- The diversity of viruses attributable to ALF cases led to low statistical power in meta-analyses conducted.
- The included studies used varying methods of virus detection including serology and molecular tests which further added to the heterogeneity in the results of our review
- Our findings show that HAV, HBV and HEV, viruses with effective vaccines, account for a large proportion of viral-induced ALF etiologies.

- Our findings support that immunization against HAV, HBV should be prioritized, especially in LMICs where resources for managing viral-induced ALF are glaringly lacking.

## MANUSCRIPT

### Background

Acute liver failure (ALF) refers to the development of encephalopathy and synthetic function impairment following acute liver injury in an individual without pre-existing liver disease (2). The presence of encephalopathy is not required to define ALF in paediatrics, but is an essential component of the definition in adults (2). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver diseases, vascular causes and/or malignancies. Acute viral hepatitis has been identified as the most common cause of ALF among all ages in Asia and Africa and one of the most common causes of ALF in children in Asia and South America (1, 3). The incidence of viral-induced ALF has substantially declined in Europe following the introduction of universal immunization against the hepatitis B virus (HBV), with only 19% of all ALF cases now attributable to viral infection in the European population (4). The introduction of routine immunization against the hepatitis A virus (HAV) in Argentina has reduced the number of hepatitis A induced ALF cases by more than 25% (4).

Fatality rates associated with ALF vary between 60% and 80%, depending on the disease etiology as well as a patient's access to care (5, 6). 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 (7). A large proportion of patients with ALF in both high and low resource settings, however, are deemed to have contraindications to transplantation or deteriorate beyond transplantation before a liver donor is found (8-10).

The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence (1). Establishing the etiology of viral-induced ALF is important for early initiation of treatment, determining the prognosis of the liver failure and identifying potential contraindications to liver transplantation. Most importantly, understanding the epidemiology of vaccine-preventable etiologies of ALF should be prioritised in under-resourced regions with limited access to facilities for transplantation. This review aims to synthesize data on the relative contribution of different viruses to the etiology of viral-induced ALF in attempt to compile evidence that is currently missing in the field.

*Bernal et al. 2010* completed a review of the burden of acute and fulminant liver failure based on literature published between 1997 and 2009. The review became the bases for guidelines for clinical practice (5). In this systematic review, we assess whether data have changed following the Bernal publication, and whether there is evidence to warrant a review of clinical practice.

**Objectives**

- To estimate the prevalence of 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), coxsackievirus (CA16) and/or adenovirus (HAdVs) among patients with ALF.
- To estimate the mortality rate for cases of 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
- To estimate the prevalence and incidence of liver transplantation for cases of 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

## Methods

This systematic review was registered with PROSPERO (registration number CRD42017079730) and the methods for its conduction have been published (11). The results of the review are reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines checklist (**Appendix 1**).

### Study eligibility criteria

Published cross-sectional, surveillance and cohort studies reporting the outcomes of interest in patients with 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 were eligible for inclusion in this study. Studies were eligible for inclusion if they had clearly stated case definitions of viral-induced ALF and confirmed ALF cases using both clinical and serological, molecular or culture diagnostic methods.

### Search strategy

A combination of the following search terms (including the use of Medical Subject Headings (MESH)) was used and adapted for each of the relevant electronic databases: 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), coxsackie virus and adenovirus.

The following electronic databases were searched for relevant literature published from 2009 to 2019: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The search was run on 9 April 2019 and updated via PubMed on 30 September 2019 with no new eligible studies to include.

**Data extraction**

Study characteristics and outcomes of interests were extracted from the included studies on a pre-designed data extraction form by two independent reviewers (JP and HH). Prior to use by the two reviewers, the reliability of the extraction form was assessed by piloting 10 randomly selected articles that met the inclusion criteria. The study team resolved any disagreements in data extraction through consensus in consultation with RM. In cases where studies were in German, HH provided translation. In cases where studies were not available in English or German, google translate was used to translate the article to English (12).

**Data synthesis and analysis**

A random-effects model was fitted to the study data as it included data taken from a series of independently performed studies in different populations. We assessed heterogeneity by calculating $I^2$ statistics (threshold $I^2 > 40\%$). The values of $I^2$ were categorized for heterogeneity as follows: “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 existed between studies ($I^2 \leq 40\%$), pooled outcome measures were reported with 95% confidence intervals for each respective outcome. Where “considerable” or “substantial” heterogeneity exists between studies ($I^2 > 40\%$), forest plots and prevalence ranges calculated using the random-effects model were used to narratively describe each outcome.

**Risk of bias assessment**

Each included study was assessed for risk of bias and quality using the Hoy *et al.,* 2012 tool for observational studies (13, 14). Studies were judged as having 'low risk' if scored 8-10, 'moderate risk' if scored 5-7 and 'high risk' if scored 0-5. All risk of bias judgements were made by both JP and HH. In case of disagreement in risk of bias and quality assessment, a final decision was made through consensus in consultation with RM.

## Results

**Patient and public involvement**

This review 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 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 was required; however, it is hoped that the findings of this review will help to highlight the burden that ALF places on populations without routine vaccination.

**Included studies**

The initial database searches yielded 6,952 records, from which 3,545 duplicates were removed. A further 3,263 were excluded following the screening of titles and abstracts (**Figure 1**). The full text of the remaining 144 records were screened by JP and HH, from which 25 studies were deemed to meet the final inclusion criteria. Twenty-four (96%) of the included studies were cohort studies. As detailed in **Table 1**, the included studies were published between 2009 and 2017. Included studies were conducted globally, with 7 studies and 3 studies conducted in India and Pakistan, respectively. The populations represented by the included studies spanned all age groups and included participants primarily from hospital settings. As the data in this review was sourced from a variety of countries, age groups and settings, the heterogeneity was considerable and/or substantial for all results. Thus, we narratively and graphically reported estimates of average prevalence rates and the spreads of prevalence.

**Vaccine-preventable viral-induced ALF**

We narratively report the prevalence of HAV- and HBV-induced ALF by country immunization status. The point prevalence of HAV-induced ALF in countries with no routine HAV immunization at the time of data collection ranged from 2% to 81% with an average of 27% (95% CI 13, 43), while the prevalence in

countries with routine HAV immunization at the time of data collection ranged from 1% to 2% with an average of 2% (95% CI 1, 3) (**Figure 2**). In Argentina, the prevalence of HAV-induced ALF prior to routine immunization was approximately 50% (95% CI 45, 55), compared to approximately 1% (95% CI 0, 5) after immunization was introduced. The point prevalence of HBV-induced ALF in countries without universal HBV immunization at the time of data collection ranged from 16% to 27% with an average of 22% (95% CI 16, 30) (**Figure 3**). The point prevalence of HBV-induced ALF in countries with universal HBV immunization at the time of data collection ranged from 0% to 83% with an average of 19% (95% CI = 7, 36).

**ALF attributable to non-vaccine-preventable viral infections**

The point prevalence of HCV-induced ALF ranged from 2% to 25% with an average of 9% (95% CI = 1, 21) (**Supplementary Figure 1**). The point prevalence of HEV-induced ALF ranged from 3% to 70% with an average of 32% (95% CI 24, 41) (**Supplementary Figure 2**). The point prevalence of HDV-, HHV/HSV-, CMV-, and EBV-induced ALF were estimated to have averages of 4% (95% CI 0, 13), 6% (95% CI 1, 12), 13% (95% CI 1, 35) and 6% (95% CI 0, 24), 10% (95% CI 2, 22), 2% (95% CI 0, 5), and 1% (95% CI 0, 5), respectively (**Supplementary Figure 3**). Data was not available to estimate the burden of ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and/or HAdVs as outlined per the published protocol (11).

**Outcomes of viral-induced ALF**

The narratively reported outcomes of viral-induced ALF were found to be severe. The mortality rates associated with viral-induced ALF in lower-middle income countries ranged from 18% to 91% with an average of 50% (95% CI 36, 64) (**Figure 4A**). The mortality rates associated with viral-induced ALF in upper-middle income countries ranged 3% to 45% with an average of 26% (95% CI 1, 63) (**Figure 4A**). The mortality rates associated with viral-induced ALF in high income countries ranged from 12% to 40% with an average of 29% (95% CI 17, 43) (**Figure 4A**). The rate of encephalopathy associated with viral-induced ALF cases in children ranged from 69% to 100% with an average of 89% (95% CI 79, 97) (**Figure 4B**). The need for liver transplantation with viral-associated ALF ranged from 4% to 62% with an average of 25% (95% CI 6, 53) (**Figure 4B**). The need for renal transplant in viral-associated ALF cases ranged from 4% to 34% with an average of 18% (95% CI 2, 43) (**Figure 4B**).

**Methodological quality**

Risk of bias scores were assigned by two reviewers (JP and HH) and are described in **Supplementary Table 1**. Overall, a majority of the included studies were judged as having 'low risk' of bias. Only one included study was judged as having 'moderate risk' of bias due to lack of clarity around the representativeness of the study population to the national population, methods of participant selection and methods employed to reduce the likelihood of non-response.

**Discussion**

This systematic review estimated the burden of ALF following infection with HAV, HBV, HCV, HEV, HSV/HHV, CMV, EBV, and parvo-virus B19. The prevalence of HAV-induced ALF is markedly lower in countries with routine HAV immunization while HEV was the most common etiological cause of viral-induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which seem to increase with poor economic status of the studied countries.

The estimated prevalence of HAV-induced ALF in countries with routine HAV immunization was markedly lower than the estimated prevalence in countries without routine HAV immunization. When looking at countries with data before and after the introduction of routine HAV immunization, the reduction of HAV-induced ALF due to vaccination is further highlighted. The average prevalence of HBV-induced ALF was the same in settings with or without universal HBV immunization. Countries without universal HBV immunization programs are likely to have weak healthcare systems; thus, the reported prevalence of HBV-induced ALF is assumed to be an underestimate of the true burden in these populations due to weak routine testing and reporting systems. Currently, there is one HEV vaccine (Hecolin) licensed in China that has shown promise with a high degree of efficacy in preventing HEV genotype IV infection in healthy individuals 16 to 65 years (15). Further exploration of the efficacy of this vaccine for prevention of infection with genotypes I and II in different populations should to explore it's application in different countries and HEV endemicity settings (16).

This review estimated the mortality rate for viral-induced ALF to be approximately 50% in low- and middle- income countries (LMICs) and less than 30% in upper-middle- and high-income countries. Previous studies have estimated that mortality rates associated with ALF vary between 60% and 80%, depending on the disease etiology as well as a patient's access to care. Our review shows that although viral-induced ALF still carries a significant mortality, though possibly lower than that reported for other ALF etiologies (5, 6). Mortality data largely comes from hospitals with the capacity to diagnose viral-

induced ALF, thus deaths outside of the hospital system or ALF deaths without virological testing may not be captured in these mortality estimates. Liver transplantation is required by approximately 25% of viral-induced ALF cases and approximately 18% of viral-induced ALF cases required renal transplantation, globally. In addition to general lack of resources for transplantation, a significant proportion of potential candidates have contraindications to transplant related to poor socioeconomic status in LMICs. The transplant data included in this review may only reflect successful and unsuccessful transplants, not those that were needed but not carried out due to resource constraints or contraindications.

This review is limited by lack of data for some of the viral etiologies of ALF including for VZV, HPIVs, YFV, CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced ALF. Additionally, we believe that our findings underestimate the global burden of viral-induced ALF as some important causes of ALF (e.g. HSV/HHV) are believed to be underrecognized as they require PCR testing for diagnosis. The included studies also used varying methods of virus detection including serology and molecular tests which further added to the heterogeneity in the results of our review. This is a well-recognized limitation in studies of ALF where diagnostics are often limited by cost in under-resourced regions where viral causes of ALF are more prevalent. The limited availability of data hindered most of the planned sub-group analyses outlined in the study protocol. Where data were available, high heterogeneity of the data led to planned meta-analyses and meta-regression analyses not being possible. Lastly, the diversity of viruses attributable to ALF cases led to low statistical power in meta-analyses conducted.

Future research should assess the burden of viral-induced ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and HAdVs. Collectively, high-quality data on all viral etiologies of ALF would allow for better pooling of results. The review team encourages future studies to incorporate health economic estimates and mathematical modelling where data permits to assist health policy decision-makers to better design strategies for the prevention and management of viral-induced ALF. Epidemiological-economic modelling of immunization against HAV, HBV and HEV may well show that introduction of vaccination could lead to future cost savings in the long run due to prevented medical care and liver failure.

**Conclusions**

We successfully addressed the aim of the study although data on VZV, HPIVs, YFV, CA16 and/or HAdVs were missing. Notwithstanding the noted limitations, it is clear that HAV, HBV and HEV – vaccine-preventable ALF etiologies – account for a large proportion of ALF (approximately 21%, 20%, 32% of viral-induced ALF cases, respectively). The burden of ALF that is associated with vaccine-preventable ALF etiologies should be used in conjunction with other available key evidence to inform practice and policies on immunization, particularly in LMICs. A majority of LMICs have established universal vaccination against HBV. The Word Health Organization has recently recommended the introduction of an HBV birth dose which is aimed at elimination of the virus and, if successful, will subsequently reduce the burden of HBV-induced ALF. Routine HAV immunization in LMICs, however, are lacking. More data is urgently needed to guide routine use of the vaccine in prevention of morbidity and mortality caused by the virus. Lastly, further applicability of HEV vaccines should be explored, especially in LMICs where resources for managing viral-induced ALF are glaringly lacking.

**Contributors**

JP, GDH, BK and RM conceived this study. JP implemented the review under the supervision of RM. JP and HSH performed the study search, screening and extraction of data under the guidance of RM. GDH and BK provided methodological expertise for this review. SS, LG, WS, and provided content expertise for this review and all authors will provided comments on the final manuscript before publication. JP is the guarantor of this review.

**Funding**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The Vaccines for Africa Initiative (VACFA) has funded the costs associated with the research and dissemination of the results, including publications.

**Competing interests**

None declared.

**Data availability**

No additional data available.

**Patient consent for publication**

Not required.

## REFERENCES


1. European Association for the Study of the Liver. Electronic address eee, Clinical practice guidelines p, Wendon J, Panel m, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047-81.
2. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012;55(3):965-7.
3. Morabito V, Adebayo D. Fulminant Hepatitis: Definitions, Causes and Management. Health. 2014;06(10):1038-48.
4. Cervio G, Trentadue J, D'Agostino D, Luque C, Giorgi M, Armoni J, et al. Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program. Hepat Med. 2011;3:99-106.
5. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet. 2010;376(Seminar):190-201.
6. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. Systematic review: acute liver failure - one disease, more than 40 definitions. Aliment Pharmacol Ther. 2012;35(11):1245-56.
7. Spearman CW, McCulloch M, Millar AJ, Burger H, Numanoglu A, Goddard E, et al. Liver transplantation at Red Cross War Memorial Children's Hospital. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2006;96(9 Pt 2):960-3.
8. O'Grady JG. Acute liver failure. Postgrad Med J. 2005;81(953):148-54.
9. O'Grady J. Liver transplantation for acute liver failure. Best Pract Res Clin Gastroenterol. 2012;26(1):27-33.
10. Patterson J, Hussey HS, Abdullahi LH, Silal S, Goddard L, Setshedi M, et al. The global epidemiology of viral-induced acute liver failure: a systematic review protocol. BMJ Open. 2019.
11. Balk E, Ching M, Chen M, Trikalinos T, L KWC. Assessing the Accuracy of Google Translate to Allow Data Extraction From Trials Published in Non-English Languages. Rockville, USA: Agency for Healthcare Research and Quality; 2013 Jan 2013. Contract No.: EHC145-EF.
12. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C. Assessing risk of bias in prevalence studies: Modification of an existing tool and evidence of interrater aggreement. Journal of Clinical Epidemiology. 2012;65:934-9.
13. Werfalli M, Musekiwa A, Engel ME, Ross I, Kengne AP, Levitt NS. The prevalence of type 2 diabetes mellitus among older people in Africa: a systematic review study protocol. BMJ Open. 2014.
14. Alam S, Azam G, Mustafa G, Azad AK, Haque I, Gani S, et al. Natural course of fulminant hepatic failure: the scenario in Bangladesh and the differences from the west. Saudi J Gastroenterol. 2009;15(4):229-33.
15. Asim MS, R.; Gupta, R. K.; Kar, P. Clinical & molecular characterization of human TT virus in different liver diseases. Indian Journal of Medical Research.131(4):545-54.
16. Bechmann LP, Manka P, Best J, Saner FH, Paul A, Canbay A, et al. Drug-induced liver injury as predominant cause of acute liver failure in a monocenter study. Deutsche Medizinische Wochenschrift. 2014;139(17):878-82.
17. Bhatia V, Dhawan A, Arora NK, Mathur P, Das MK, Irshad M. Urinary potassium loss in children with acute liver failure and acute viral hepatitis. J Pediatr Gastroenterol Nutr. 2013;57(1):102-8.
18. Borkakoti JH, R. K.; Mohammad, A.; Kumar, A.; Kar, P. Does high viral load of hepatitis E virus influence the severity and prognosis of acute liver failure during pregnancy? Journal of Medical Virology. 2013;85(4):620-6.
19. Bravo LC, Gregorio GV, Shafi F, Bock HL, Boudville I, Liu Y, et al. Etiology, incidence and outcomes of acute hepatic failure in 0-18 year old Filipino children. Southeast Asian J Trop Med Public Health. 2012;43(3):764-72.
20. Das AK, Begum T, Kar P, Dutta A. Profile of Acute Liver Failure from North-east India and Its Differences from other Parts of the Country. Euroasian J Hepatogastroenterol. 2016;6(2):111-5.
21. Gupta P, Mittal M, Bhat NK, Agarwal RK, Gupta P, Mittal G. A hospital based retrospective study on hepatotropic viruses as a cause of acute viral hepatitis in children in Uttarakhand, India. Indian Journal of Community Health. 2015;27(4):451-5.
22. Ho CM, Lee CH, Wang JY, Lee PH, Lai HS, Hu RH. Nationwide longitudinal analysis of acute liver failure in taiwan. Medicine (Baltimore). 2014;93(4):e35.
23. Latif N, Mehmood K. Risk factors for fulminant hepatic failure and their relation with outcome in children. J Pak Med Assoc. 2010;60(3):175-8.
24. Mamun Al M, Rahman S, Khan M, Karim F. HEV infection as an aetiologic factor for acute hepatitis: experience from a tertiary hospital in Bangladesh. J Health Popul Nutr. 2009;27(1):14-9.
25. Manka P, Bechmann LP, Coombes JD, Thodou V, Schlattjan M, Kahraman A, et al. Hepatitis E Virus Infection as a Possible Cause of Acute Liver Failure in Europe. Clin Gastroenterol Hepatol. 2015;13(10):1836-42.e2; quiz e157-8.
26. Mendizabal MM, S.; Videla, M. G.; Anders, M.; Zerega, A.; Balderramo, D. C.; Chan, D.; Barrabino, M.; Gil, O.; Mastai, R.; Yantorno, S.; Gadano, A.; Silva, M. O. Changing etiologies and outcomes of acute liver failure: Perspectives from 6 transplant centers in Argentina. Liver Transplantation. 2014;20(4):483-9.
27. Mishra SB, J.; Kumar, S.; Kar, P. Role of HEV antigen detection in HEV-related acute viral hepatitis and acute liver failure. Journal of Medical Virology. 2016;88(12):2179-85.

28. Mumtaz K, Azam Z, Hamid S, Abid S, Memon S, Ali Shah H, et al. Role of N-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. Hepatology International. 2009;3(4):563-70.
29. Pandit A, Mathew LG, Bavdekar A, Mehta S, Ramakrishnan G, Datta S, et al. Hepatotropic viruses as etiological agents of acute liver failure and related-outcomes among children in India: a retrospective hospital-based study. BMC Res Notes. 2015;8:381.
30. Poovorawan Y, Chongsrisawat V, Shafi F, Boudville I, Liu Y, Hutagalung Y, et al. Acute hepatic failure among hospitalized Thai children. Southeast Asian J Trop Med Public Health. 2013;44(1):50-3.
31. Schwarz KBO, Dominic Dell; Lobritto, Steven J.; Lopez, M. James; Rodriguez-Baez, Norberto; Yazigi, Nada A.; Belle, Steven H.; Zhang, Song; Squires, Robert H.; for the Pediatric Acute Liver Failure Study, Group. Analysis of Viral Testing in Nonacetaminophen Pediatric Acute Liver Failure. Journal of Pediatric Gastroenterology & Nutrition. 2014;59(5):616-23.
32. Shalimar, Kedia S, Gunjan D, Sonika U, Mahapatra SJ, Nayak B, et al. Acute Liver Failure Due to Hepatitis E Virus Infection Is Associated with Better Survival than Other Etiologies in Indian Patients. Dig Dis Sci. 2017;62(4):1058-66.
33. Silverio CE, Smithen-Romany CY, Hondal NI, Diaz HO, Castellanos MI, Sosa O. Acute liver failure in Cuban children. MEDICC Rev. 2015;17(1):48-54.
34. Somasekar SL, D.; Rule, J.; Naccache, S. N.; Stone, M.; Busch, M. P.; S.; ers, C.; Lee, W. M.; Chiu, C. Y. Viral Surveillance in Serum Samples from Patients with Acute Liver Failure by Metagenomic Next-Generation Sequencing. Clinical Infectious Diseases. 2017;65(9):1477-85.
35. Uddin Jamro BMC, S.; Mal Makheja, P.; Ahmed Soomro, A. Etiology, outcome and risk factors for fulminant hepatic failure in children at a tertiary care hospital, Sukkur, Pakistan. Rawal Medical Journal. 2013;38(3):219-22.
36. Tsunoda T, Inui A, Iwasawa K, Oikawa M, Sogo T, Komatsu H, et al. Acute liver dysfunction not resulting from hepatitis virus in immunocompetent children. Pediatr Int. 2017;59(5):551-6.
37. Zhao P, Wang CY, Liu WW, Wang X, Yu LM, Sun YR. Acute liver failure in Chinese children: a multicenter investigation. Hepatobiliary Pancreat Dis Int. 2014;13(3):276-80.
38. Li SW, Zhao Q, Wu T, Chen S, Zhang J, Xia NS. The development of a recombinant hepatitis E vaccine HEV 239. Hum Vaccin Immunother. 2015;11(4):908-14.
39. Wu X, Chen P, Lin H, Hao X, Liang Z. Hepatitis E virus: Current epidemiology and vaccine. Human Vaccines and Immunotherapeutics. 2016;12(10):2603-10.

## FIGURE LEDENDS

Figure 1
PRISMA Flow Diagram describing selection of studies.

Figure 2
Abbreviations: HAV = hepatitis A virus, ALF = acute liver failure, CI = confidence interval, I2 = heterogeneity statistic

Figure 3
Abbreviations: HBV = hepatitis B virus, ALF = acute liver failure, CI = confidence interval, I2 = heterogeneity statistic

Figure 4
Abbreviations: ALF = acute liver failure, CI = confidence interval, I2=heterogeneity statistic, NA = not applicable

## TABLES

**Table 1: Characteristics of included studies**

| Study | Study Design | Aim | Country | Income Level | Start of Data Collection | End of Data Collection | ALF Case Definition |
|---|---|---|---|---|---|---|---|
| Alam et al., 2009 (14) | Prospective cohort | To evaluate the etiology, complications, and outcome of FHF | Bangladesh | Lower-middle | 3-Nov | 8-May | Occurrence of hepatic encephalopathy within 8 weeks of onset of jaundice in patients with no previous liver disease and the presence of coagulopathy as proved by a PT > 15 s or INR > 1.5 |
| Asim et al., 2009 (15) | Cross-sectional | To analyze serum samples from patients with ALF for hepatitis A-G viral markers | India | Lower-middle | 1-Jun | 4-May | Patient become deeply jaundiced and went into hepatic encephalopathy within 8 weeks of onset of the disease, with no past history of chronic hepatitis |
| Bechmann et al., 2014 (16) | Retrospective cohort | To identify currently predominant etiologies of ALF at a transplant center | Germany | High | 1-Jan | 12-Feb | *Acute Liver Failure Study Group Germany* case definition: INR > 1.5 and encephalopathy of any grade. Pre-existing liver disease and systemic cause of liver failure were excluded |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Bhatia et al., 2013 (17) | Prospective cohort | To analyze clinical features, liver function tests, hepatitis viral markers and clinical outcomes in patients with ALF | India | Lower-middle | Jun-99 | 1-Jan | Development of hepatic encephalopathy within 26 weeks of the first symptoms of acute hepatitis-like illness without any history of underlying liver disease |
| Borkakoti et al., 2013 (18) | Prospective cohort | To determine the viral load of HEV and its association with the disease severity in patients with ALF in comparison with patients with ALF due to other hepatides | India | Lower-middle | 6-Jan | 11-Dec | Development of encephalopathy within 8 weeks of the onset of jaundice without any past history of chronic liver disease; diagnosed as a self-limiting disease and a serum aspartate aminotransferase elevation of at least fivefold or clinical jaundice or both |
| Bravo et al., 2012 (19) | Prospective & retrospective cohort | To investigate the etiology, outcomes and incidence of AHF among children 0-18 years old | Philippines | Lower-middle | Jan-00 | 6-Dec | Onset of coagulopathy and/or encephalopathy ≤4 weeks after the onset of symptoms, a prothrombin time > 2, an increased bilirubin and evidence for liver failure complicated by encephalopathy |
| Cervio et al., 2011 (4) | Retrospective cohort | To investigate the impact of HAV UI on the trends in the occurrence of FHF in children | Argentina | High | Mar-93 | 5-Jul | *Mieli-Vergani* case definition: a multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in a patient with or without recognized underlying chronic liver disease (**Cheeseman & Mieli-Vergani, 2004**) |
| Das et al., 2016 (20) | Prospective cohort | To determine the profile of ALF etiologies | India | Lower-middle | 7-Jan | 15-Dec | History of development of encephalopathy within 8 weeks of disease onset |
| Gupta et al., 2015 (21) | Retrospective cohort | To determine the profile of Hepatitis A, B, C and E as a cause of AHF in children in a | India | Lower-middle | 11-Jan | 14-Dec | Elevated ALT levels or AST of at least five-fold with clinical jaundice and without evidence of chronic liver disease. Patients who had INR > 1.5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | tertiary care hospital | | | | | with encephalopathy or INR > 2 without encephalopathy |
| Ho et al., 2014 (22) | Prospective cohort | To investigate the incidence, etiology, outcomes, and prognostic factors of ALF | Taiwan | High income | 5-Jan | 7-Sep | International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 570.0 |
| Latif et al., 2010 (23) | Prospective cohort | To identify the risk factors for FHF and their relationship with the outcome in children | Pakistan | Lower-middle | 6-Sep | 7-Feb | Development of encephalopathy within 8 weeks of the onset of jaundice having evidence of coagulopathy i.e. PT deranges > 4 s of control and deranged liver function i.e. TSB > 1.5 mg/dl, AT > 40 IU/L |
| Mamun et al., 2009 (24) | Retrospective cohort | To assess the burden of HEV as a cause of ALF | Bangladesh | Lower-middle | 4-Jun | 6-Dec | Previously healthy patients who presented with severe impairment of hepato-cellular function, i.e. encephalopathy, coagulopathy, and jaundice, within six months of onset of symptoms |
| Manka et al., 2015 (25) | Retrospective cohort | To investigate the causes of previously diagnosed indeterminate cases ALF | Germany | High | 6-Nov | 13-Dec | Significant liver dysfunction with pathologically increased laboratory parameters [AST, ALT, AP], an existing coagulopathy in terms of an INR > 1.5, and with the concomitant presence of any degree of encephalopathy |
| Mendizabal et al., 2014 (26) | Retrospective cohort | To determine the causes and short-term outcomes of ALF | Argentina | High | 5-Jun | 11-Dec | Presence of coagulopathy [INR > 1.5 or prothrombin index < 50%] and any grade of HE within 26 weeks of the first symptoms without a known underlying liver disease |
| Mishra et al., 2016 (27) | Retrospective cohort | To assess the relative efficacy of HEV antigen detection by | India | Lower-middle | 13-Nov | 15-Jan | Any evidence of coagulation abnormality, generally INR >1.5 and any degree of mental alteration (encephalopathy) without pre- |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | ELISA in patients with ALF | | | | | existing cirrhosis and with an illness of < 4 weeks duration |
| Mumtaz et al., 2009 (28) | Prospective cohort compared to historical control | To assess the etiology, prothrombin time (PT), alanine aminotransferase, creatinine, albumin for non-acetaminophen-induced ALF | Pakistan | Lower middle | Jan-00 | 7-Mar | Rapid development of acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver |
| Pandit et al., 2015 (29) | Retrospective cohort | To assess the frequency of hepatotropic viruses as etiological agents of ALF | India | Lower-middle | 3-Jan | 5-Dec | Onset of encephalopathy ≤28 days after the onset of symptoms with INR > 2 and increased bilirubin complicated by encephalopathy in patients without a previous history of liver disease |
| Poovorawan et al., 2013 (30) | Prospective cohort | To determine the causes and outcomes of Thai children with AHF | Thailand | Upper-middle | 2-Jan | 5-Sep | *International Association for the Study of the Liver* case definition: **(Tandon et al, 1999)** |
| Schwarz et al., 2014 (31) | Retrospective cohort - Patient registry | To analyzed results of viral testing among non-acetaminophen ALF study participants | USA/Canada/UK | High | Dec-99 | 12-Dec | No known evidence of chronic liver disease, with evidence of acute liver injury, and hepatic-based coagulopathy not corrected by vitamin K with the follow parameters: PT ≥ 15 s or INR ≥ 1.5 in the presence of clinical HE or a PT ≥ 20 s or INR ≥ 2.0 regardless of the presence or absence of clinical HE |
| Shalimar et al., 2017 (32) | Retrospective cohort | To assess the differences in the course of HEV-ALF as compared to other etiologies of ALF | India | Lower middle | Jan-86 | 15-Dec | *International Association for the Study of Liver* (IASL) case definition: Occurrence of encephalopathy within 4 weeks from the onset of symptoms in the absence of preexisting liver disease |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Silverio et al., 2015 (33) | Retrospective cohort | To describe the clinical features of children treated for ALF | Cuba | Upper-middle | 5-Jan | 11-Dec | Evidence of liver damage in the absence of prior known chronic liver disease; altered coagulation, expressed as PT >15 s with encephalopathy; or PT > 20 s with or without encephalopathy—all this within eight weeks of onset of clinical symptoms |
| Somasekar et al., 2017 (34) | Retrospective cohort | To investigate the causes of previously diagnosed indeterminate cases ALF | United States | High | Jan-98 | 10-Dec | *United States Acute Liver Failure Study Group* case definition |
| Uddin Jamro et al., 2013 (35) | Retrospective cohort | To study the etiology, outcome and risk factors for FHF in children at a tertiary care hospital | Pakistan | Lower-middle | 7-Jul | 12-Jun | Presence of acute liver failure (coagulopathy PT > 20 s or INR > 2), HE without pre-existing liver disease, within 8 weeks of the onset of clinical liver disease |
| Tsunoda et al., 2017 (36) | Prospective cohort | To identify the roles of CMV, EBV and HHV in immunocompetent children with acute liver failure not resulting from hepatitis virus | Japan | High | 7-Jan | 13-Dec | Liver dysfunction with elevated AST and ALT > 30 IU/L |
| Zhao et al., 2014 (37) | Retrospective cohort | To investigate etiologies and outcomes of children with ALF | China | Middle | 7-Jan | 12-Dec | Coagulopathy [PTA ≤40% or INR ≥ 1.5 excluding hematologic diseases] and jaundice [Tbil ≥ 171 μmol/L] within 4 weeks in a child without pre-existing liver diseases |

**Abbreviations:** ALF = acute liver failure; FHF = fulminant hepatic failure; AHF = acute hepatic failure; HEV = hepatitis E virus; CMV = cytomegalovirus; EBV = Epstein Barr virus; HHV = human herpesvirus; ELISA = enzyme-linked immunosorbent assay; INR = international normalized ratio; PT = prothrombin time; s = second; TSB = total serum bilirubin; HE = hepatic encephalopathy; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP = alkaline phosphatase; PTA = plasma thromboplastin antecedent

Figure 1: Flow diagram for selection of studies

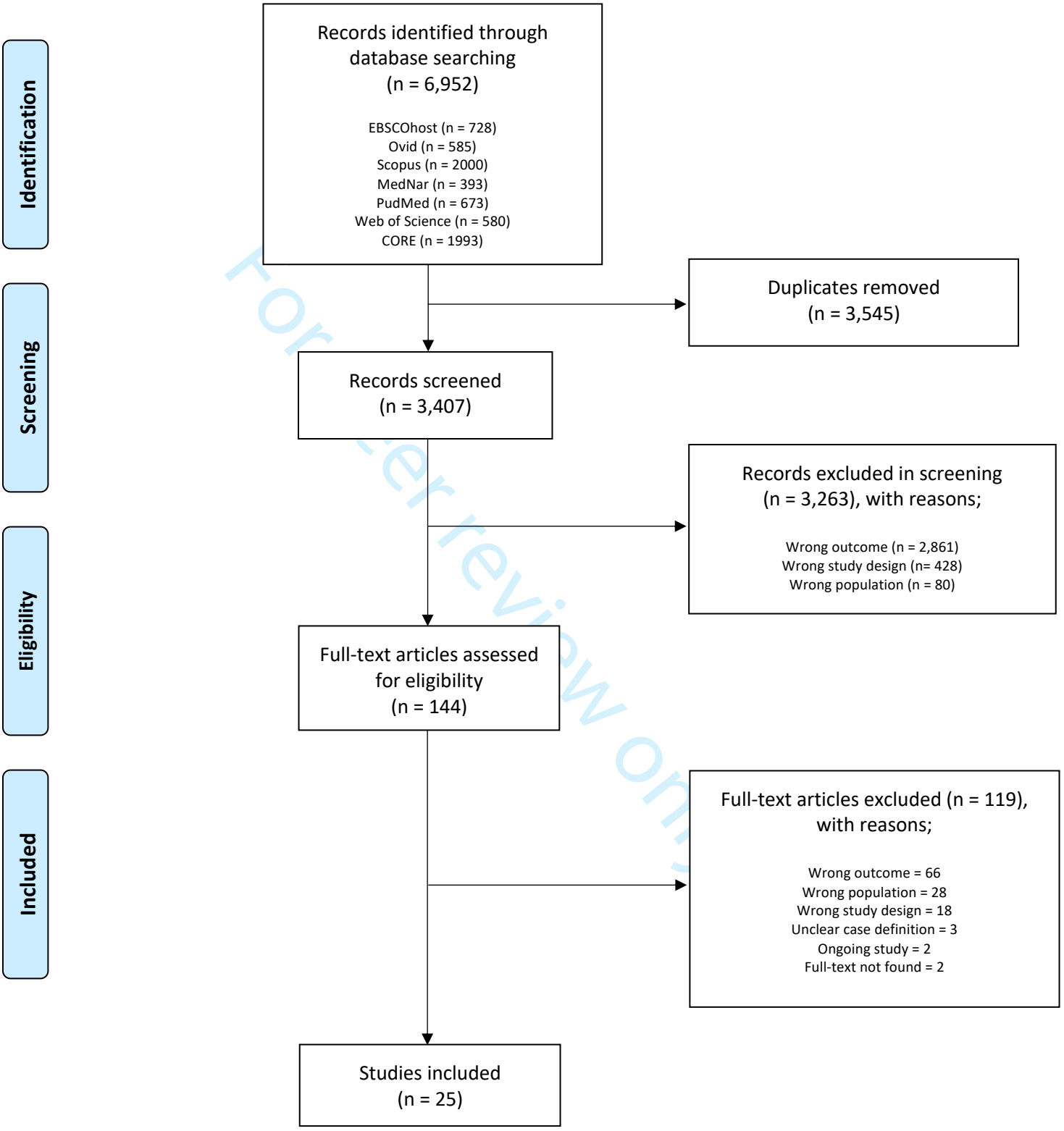


Figure 2: Prevalence of HAV-induced ALF by country HAV immunization status

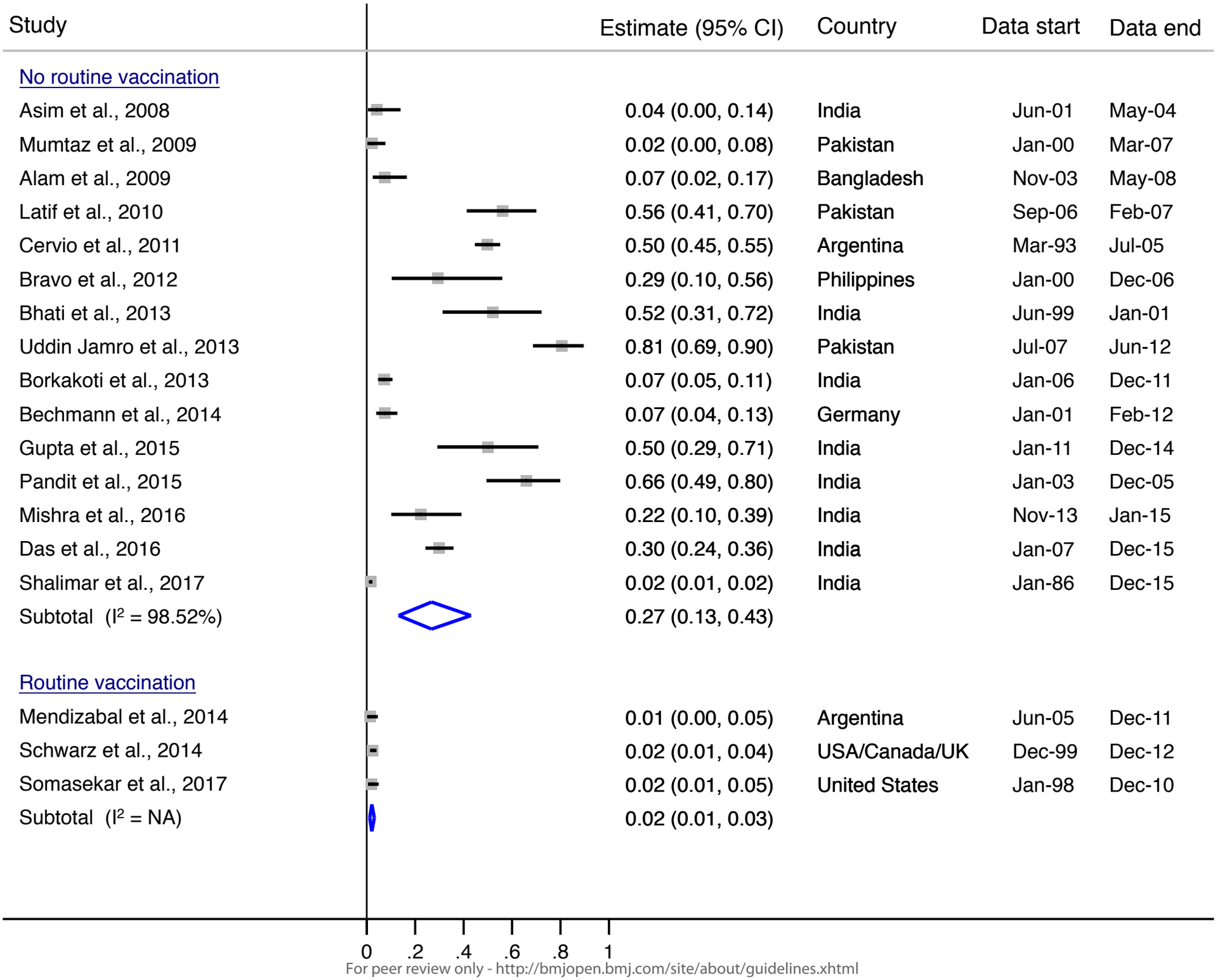
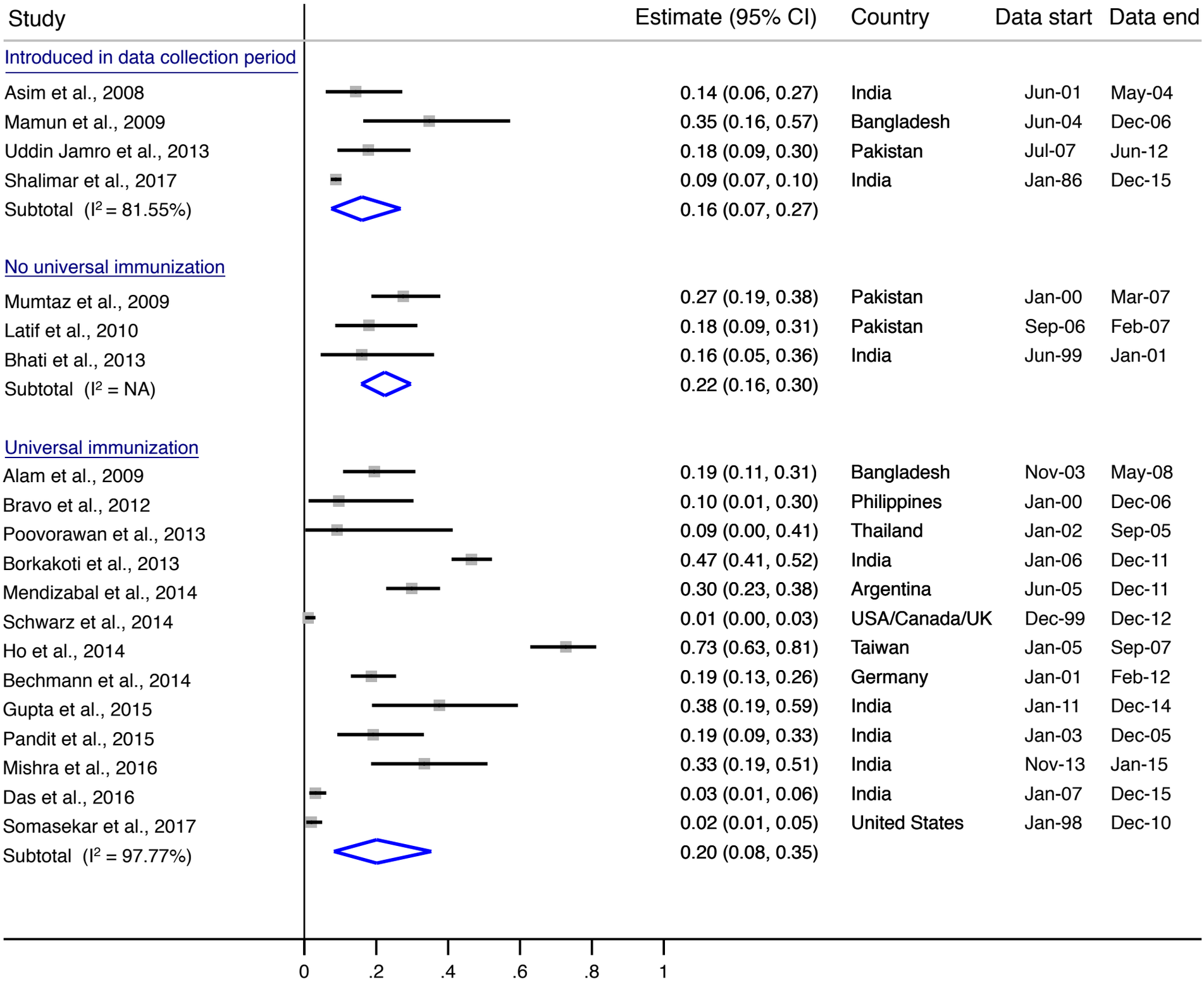
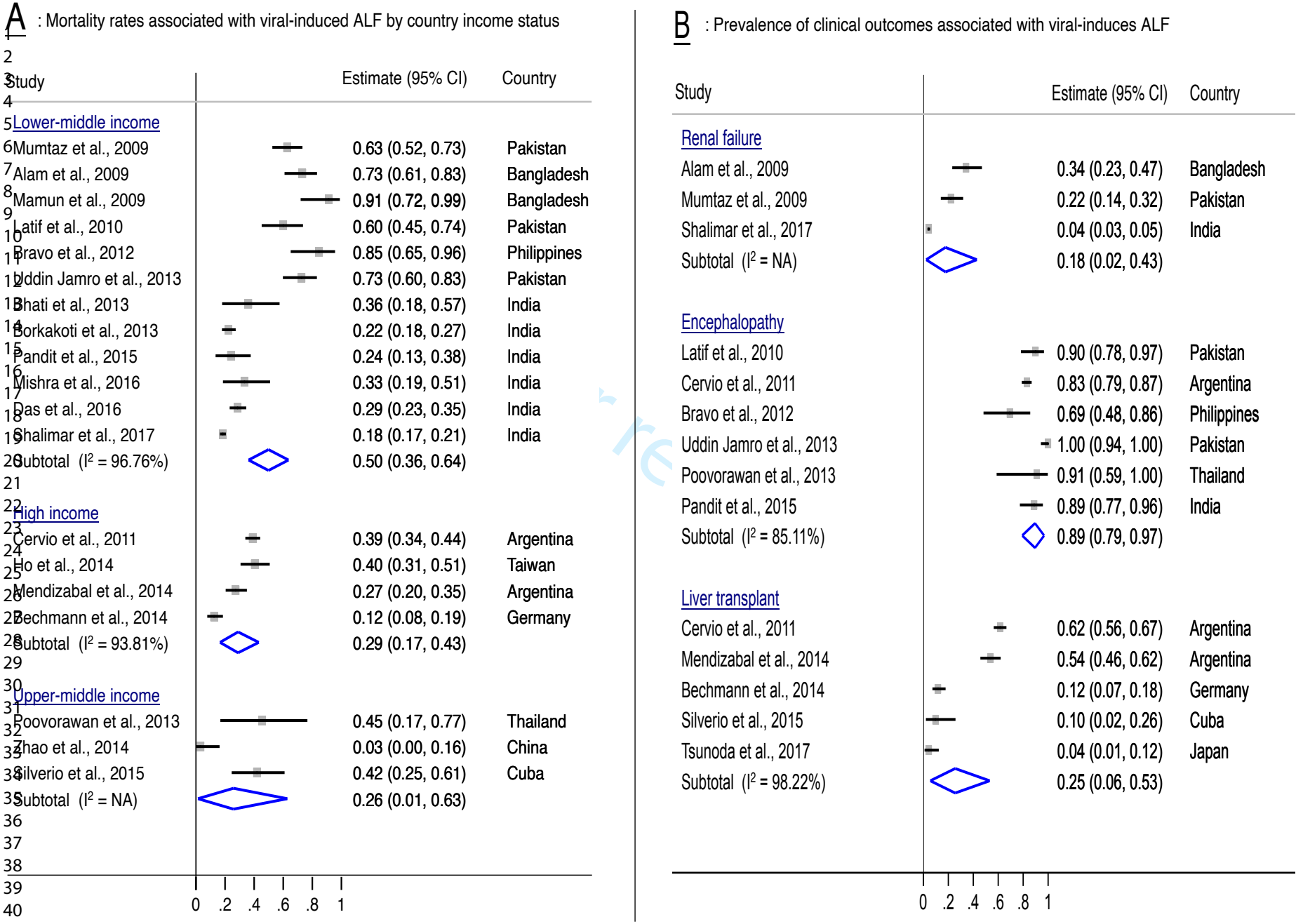


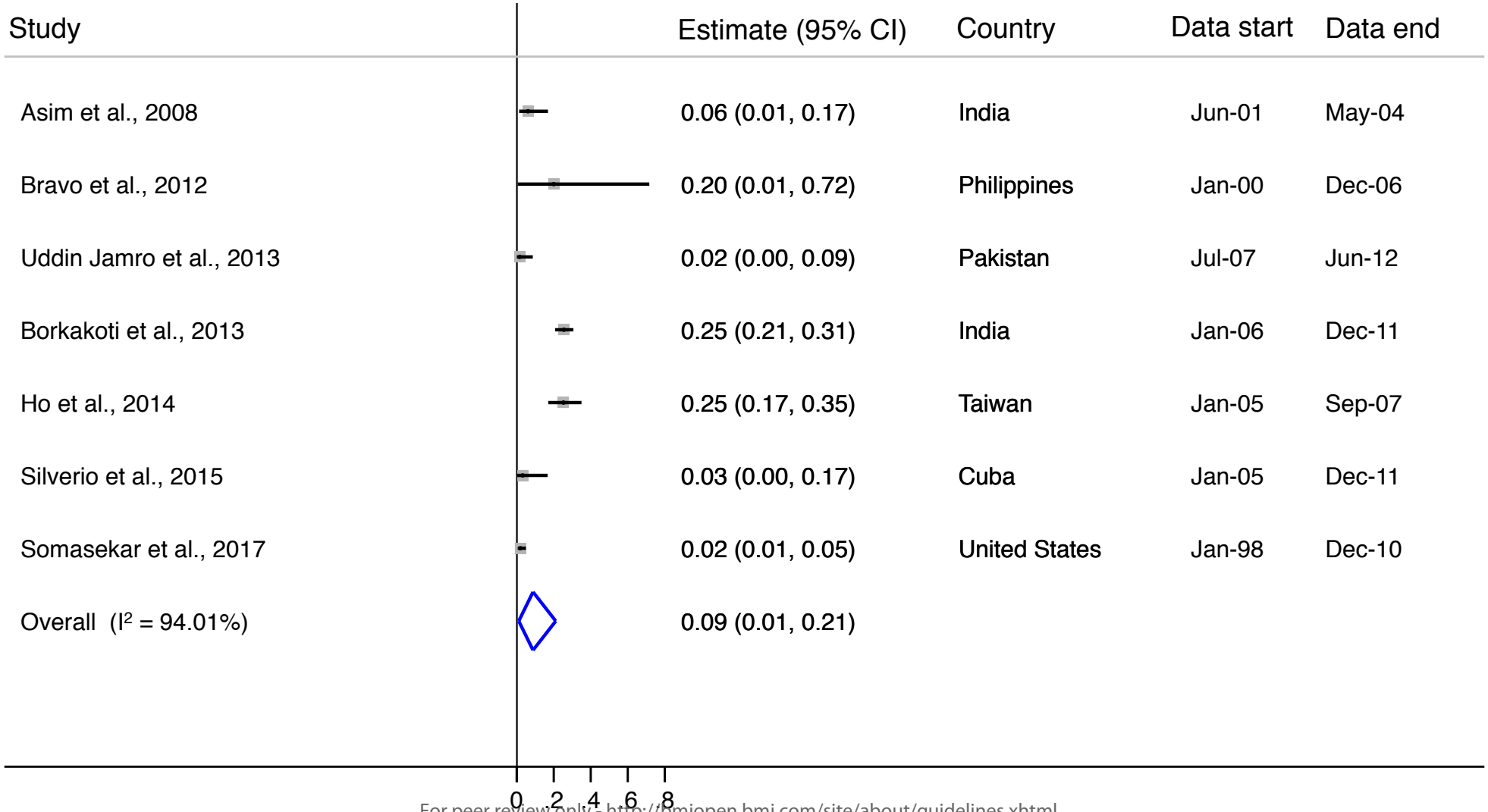
Figure 3: Prevalence of HBV-induced ALF by country HBV immunization status



# Figure 4: Prevalence of outcomes associated with viral-induced ALF



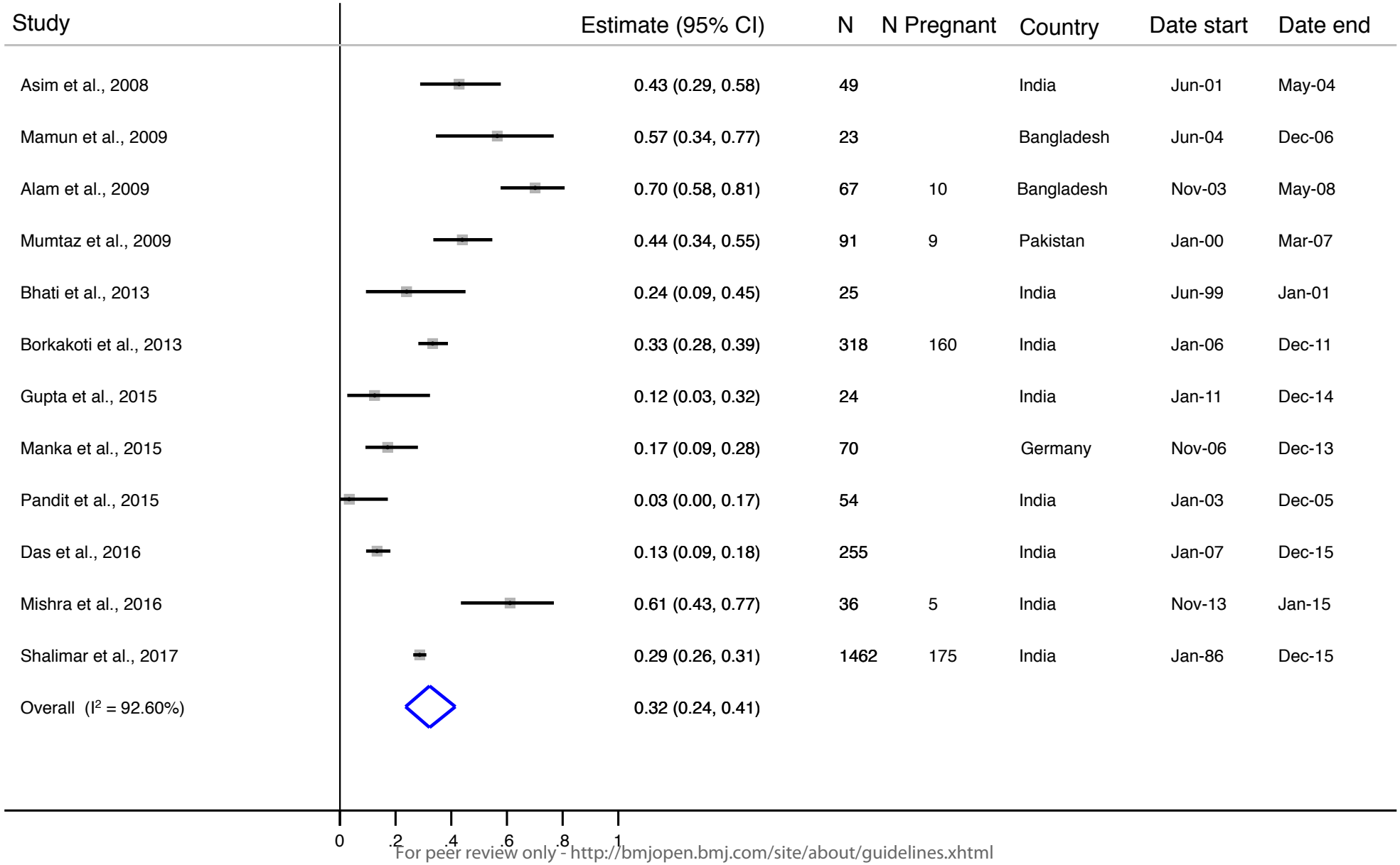
# Supplementary Figure 1: Prevalence of HCV-induced ALF






Abbreviations: HCV = hepatitis C virus, ALF = acute liver failure, CI = confidence interval, $I^2$ = heterogeneity statistic

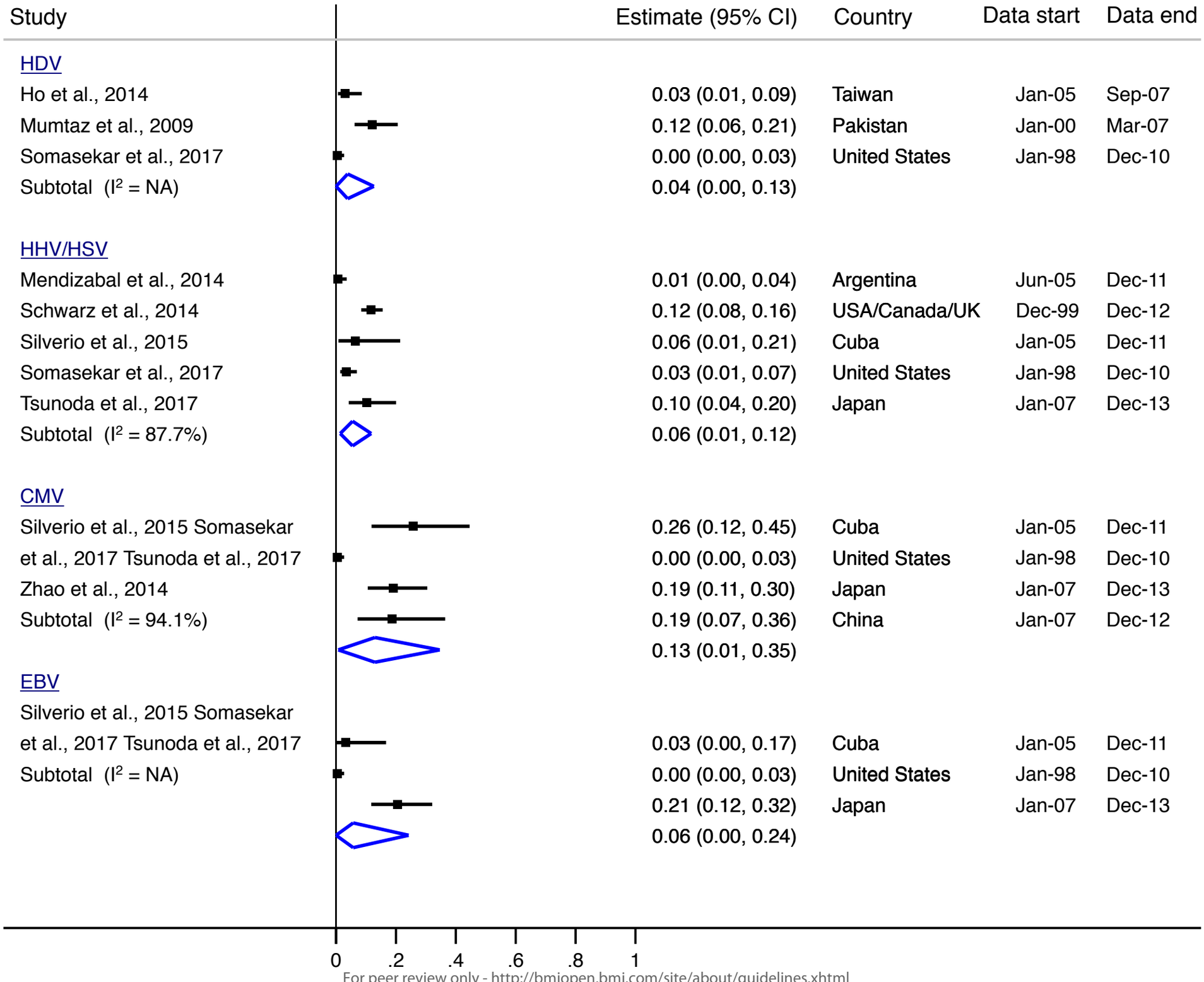
# Supplementary Figure 2: Prevalence of HEV-induced ALF






Abbreviations: HEV = hepatitis E virus, ALF = acute liver failure, CI = confidence interval, $I^2$ = heterogeneity statistic

# Supplementary Figure 3: Prevalence of HDV-, HHV/HSV-, CMV- and EBV-induced AFL






Abbreviations: HDV = hepatitis D virus, HHV/HSV = Human Herpes virus/Herpes Simplex Virus, CMV = Cytomegalovirus, EBV = Epstein-Barr virus, ALF = acute liver failure, CI = confidence interval, I = heterogeneity statistic

## SUPPLEMENTARY TABLE

**Supplementary Table 1: Risk of bias judgements for included studies**

| Study ID | Representation of the national population | Representation of target population | Random selection or census | Minimal likelihood of non-response bias | Data collected directly from participants | Acceptable case definition | Valid measurement | Same mode of data collection | Appropriate length | Appropriate numerator(s) and denominator(s) | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alam et al., 2009 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Asim et al., 2009 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Bechmann et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Bhati et al., 2013 | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Borkakoti et al., 2013 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Bravo et al., 2012 | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Cervio et al., 2011 | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Das et al., 2016 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Gupta et al., 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Ho et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Latif et al., 2010 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Mamun et al., 2009 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Manka et al., 2015 | No | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | 8 |
| Mendizabal et al., 2014 | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Mishra et al., 2016 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 7 |
| Mumtaz et al., 2009 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Pandit et al., 2015 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Poovorawan et al., 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 9 |
| Schwarz et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 9 |
| Shalimar et al., 2017 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Silverio et al., 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Somasekar et al., 2017 | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Uddin Jamro et al., 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Tsunoda et al., 2017 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Zhao et al., 2014 | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |

BMJ Open

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

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-037473.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 14-Apr-2020 |
| Complete List of Authors: | Patterson, Jenna; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Hussey, Hannah; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health & Family Medicine<br>Silal, Sheetal; University of Cape Town, Department of Statistical Sciences; University of Oxford, Nuffield Department of Medicine<br>Goddard, Liz; University of Cape Town, Department of Paediatrics, Red Cross War Memorial Children's Hospital<br>Setshedi, Mashiko; University of Cape Town, Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital<br>Spearman, Wendy ; University of Cape Town, Department of Medicine, Division of Hepatology, Groote Schuur Hospital<br>Hussey, Gregory; University of Cape Town Faculty of Health Sciences, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Kagina, Benjamin; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Muloiwa, Rudzani; University of Cape Town, 5Department of Pediatrics & Child Health, Red Cross War Memorial Children’s Hospital; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiaitve, School of Public Health and Family Medicine |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Infectious diseases |
| Keywords: | Epidemiology < INFECTIOUS DISEASES, Hepatology < INTERNAL MEDICINE, VIROLOGY |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

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

Jenna Patterson[1,2], Hannah Sophia Hussey[1,2], Sheetal Silal[3,4], Liz Goddard[5], Mashiko Setshedi[6], C. Wendy Spearman[7], Gregory D. Hussey[1,8] Benjamin M. Kagina[1,2] and Rudzani Muloiwa[1,5]

[1]Vaccines for Africa Initiative, University of Cape Town, South Africa

[2]School of Public Health & Family Medicine, University of Cape Town, South Africa

[3]Modelling and Simulation Hub, Africa, Department of Statistical Sciences, Faculty of Science, University of Cape Town, South Africa

[4]Nuffield Department of Medicine, Oxford University, Oxford, United Kingdom

[5]Department of Pediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town

[6]Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital, University of Cape Town, South Africa

[7]Division of Hepatology, Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital, South Africa

[8]Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa

[5]Department of Pediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town

*Corresponding author*: Jenna Patterson

*Corresponding author's ORCID iD:* 0000-0002-3927-037X

*Corresponding author's email address*: pttjen005@myuct.ac.za

*Corresponding author's postal address:* Vaccines for Africa Initiative, Room N2.09A, Werner Beit North, Health Sciences Campus, Anzio Road, Observatory, 7925

*H.S. Hussey email address:* hshussey@gmail.com

*S. Silal email address:* sheetal.silal@uct.ac.za

*E. Goddard email address:* liz.goddard@uct.ac.za

*M. Setshedi email address:* mashiko.setshedi@uct.ac.za

*W. Spearman email address:* wendy.spearman@uct.ac.za

*G.D. Hussey email address:* gregory.hussey@uct.ac.za

*B.M. Kagina email address:* benjamin.kagina@uct.ac.za

*R. Muloiwa email address:* rudzani.muloiwa@uct.ac.za

## REQUIRED STATEMENTS

**Funding statement**

This project was not supported by any funding source.

**Conflict of interest disclosure**

All authors have no conflicts of interest to declare.

**Ethics approval statement**

This study did not require ethics approval as it uses publicly available, published data.

**Patient consent statement**

This study did not require consent from patients as it uses no individual data.

**Permission to reproduce material from other sources**

This study has cited all references which are published and publicly available.

## ABBREVIATIONS

- Acute liver failure (ALF)
- 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)
- Human parainfluenza viruses (HPIVs)
- Yellow fever virus (YFV)
- Human herpesvirus 6 (HHV-6)
- Cytomegalovirus (CMV)
- Coxsackievirus (CA16)
- Adenovirus (HAdVs)
- Medical Subject Headings (MESH)
- Low- and middle- income countries (LMICs)

## ABSTRACT

**Objectives:** The etiology and burden of viral-induced acute liver failure (ALF) remains unclear, globally. It is important to understand the epidemiology of viral-induced ALF to plan for clinical case management and case prevention.

**Participants:** This systematic review was conducted to synthesize data on the relative contribution of different viruses to the etiology of viral-induced ALF in attempt to compile evidence that is currently missing in the field. Five electronic databases were searched for relevant literature from 2009 to 2019. Twenty-five eligible studies were included in the results of this review.

**Results:** This systematic review estimated the burden of acute liver failure following infection with HBV, HAV, HBV, HCV, HEV, HSV/HHV, CMV, EBV, and parvo-virus B19. Data were largely missing for ALF following infection with VZV, HPIVs, YFV, CA16 and/or HAdVs. The prevalence of HAV-induced ALF was markedly lower in countries with routine HAV immunization vs no routine HAV immunization. Hepatitis E virus was the most common etiological cause of viral-induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which appear to increase with poor economic status of the studied countries.

**Conclusions:** Immunization against HAV and HBV should be prioritized in LMICs to prevent high viral-induced ALF mortality rates, especially in settings where resources for managing acute liver failure are lacking. The expanded use of HEV immunization should be explored as HEV was the most common cause of ALF.

**Registration:** PROSPERO registration number CRD42017079730


**Strengths and limitations**

- Our findings show that HAV, HBV and HEV, viruses with effective vaccines, account for a large proportion of viral-induced ALF etiologies.
- The study identifies a specific virus, Hepatitis E, as the most common etiological cause of viral-induced ALF.
- Findings are limited by lack of data for some of the viral etiologies of ALF including for VZV, HPIVs, YFV, CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced ALF.
- The diversity of viruses attributable to ALF cases and viral detection methods led to high heterogeneity and low statistical power in meta-analyses conducted.

- Our findings support that immunization against HAV, HBV should be prioritized, especially in LMICs where resources for managing viral-induced ALF are glaringly lacking.

## MANUSCRIPT

### Background

Acute liver failure (ALF) refers to the development of encephalopathy and synthetic function impairment following acute liver injury in an individual without pre-existing liver disease (1). The presence of encephalopathy is not required to define ALF in paediatrics, but is an essential component of the definition in adults (1). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver diseases, vascular causes and/or malignancies. Acute viral hepatitis has been identified as the most common cause of ALF among all ages in Asia and Africa and one of the most common causes of ALF in children in Asia and South America (2, 3). The incidence of viral-induced ALF has substantially declined in Europe following the introduction of universal immunization against the hepatitis B virus (HBV), with only 19% of all ALF cases now attributable to viral infection in the European population (4). The introduction of routine immunization against the hepatitis A virus (HAV) in Argentina has reduced the number of hepatitis A induced ALF cases by more than 25% (4).

Fatality rates associated with ALF vary between 60% and 80%, depending on the disease etiology as well as a patient's access to care (5, 6). 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 (7). A large proportion of patients with ALF in both high and low resource settings, however, are deemed to have contraindications to transplantation or deteriorate beyond transplantation before a liver donor is found (8-10).

The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence (3). Establishing the etiology of viral-induced ALF is important for early initiation of treatment, determining the prognosis of the liver failure and identifying potential contraindications to liver transplantation. Most importantly, understanding the epidemiology of vaccine-preventable etiologies of ALF should be prioritised in under-resourced regions with limited access to facilities for transplantation. This review aims to synthesize data on the relative contribution of different viruses to the etiology of viral-induced ALF in attempt to compile evidence that is currently missing in the field.

*Bernal et al. 2010* completed a review of the burden of acute and fulminant liver failure based on literature published between 1997 and 2009. The review became the bases for guidelines for clinical practice (5). In this systematic review, we assess whether data have changed following the Bernal publication, and whether there is evidence to warrant a review of clinical practice.

**Objectives**

- To estimate the prevalence of 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), coxsackievirus (CA16) and/or adenovirus (HAdVs) among patients with ALF.
- To estimate the mortality rate for cases of 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
- To estimate the prevalence and incidence of liver transplantation for cases of 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

## Methods

This systematic review was registered with PROSPERO (registration number CRD42017079730) and the methods for its conduction have been published (11). The results of the review are reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines checklist.

**Study eligibility criteria**

Published cross-sectional, surveillance and cohort studies reporting the outcomes of interest in patients with 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 were eligible for inclusion in this study. Studies were eligible for inclusion if they had clearly stated case definitions of viral-induced ALF and confirmed ALF cases using both clinical and serological, molecular or culture diagnostic methods.

**Search strategy**

A combination of the following search terms (including the use of Medical Subject Headings (MESH)) was used and adapted for each of the relevant electronic databases: 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), coxsackie virus and adenovirus.

The following electronic databases were searched for relevant literature published from 2009 to 2019: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The search was run on 9 April 2019 and updated via PubMed on 30 September 2019 with no new eligible studies to include.

**Data extraction**

Study characteristics and outcomes of interests were extracted from the included studies on a pre-designed data extraction form by two independent reviewers (JP and HH). Prior to use by the two reviewers, the reliability of the extraction form was assessed by piloting 10 randomly selected articles that met the inclusion criteria. The study team resolved any disagreements in data extraction through consensus in consultation with RM. In cases where studies were in German, HH provided translation. In cases where studies were not available in English or German, google translate was used to translate the article to English (12).

**Data synthesis and analysis**

A random-effects model was fitted to the study data as it included data taken from a series of independently performed studies in different populations. We assessed heterogeneity by calculating $I^2$ statistics (threshold $I^2 > 40\%$). The values of $I^2$ were categorized for heterogeneity as follows: “not important” ($\leq$ 40%), “moderate” ($>$ 40% to $\leq$ 60%) and “considerable” ($>$ 60% to $\leq$ 80%) and “substantial” ($>$ 80% to $\leq$ 100%). Where “not important” or “moderate” heterogeneity existed between studies ($I^2 \leq 40\%$), pooled outcome measures were reported with 95% confidence intervals for each respective outcome. Where “considerable” or “substantial” heterogeneity exists between studies ($I^2 > 40\%$), forest plots and prevalence ranges calculated using the random-effects model were used to narratively describe each outcome.

**Risk of bias assessment**

Each included study was assessed for risk of bias and quality using the Hoy *et al.,* 2012 tool for observational studies (13, 14). Studies were judged as having 'low risk' if scored 8-10, 'moderate risk' if scored 5-7 and 'high risk' if scored 0-5. All risk of bias judgements were made by both JP and HH. In case of disagreement in risk of bias and quality assessment, a final decision was made through consensus in consultation with RM.

**Patient and public involvement**

This review 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 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 was required; however, it is hoped that the findings of this review will help to highlight the burden that ALF places on populations without routine vaccination.

## Results

The initial database searches yielded 6,952 records, from which 3,545 duplicates were removed. A further 3,263 were excluded following the screening of titles and abstracts (**Figure 1**). The full text of the remaining 144 records were screened by JP and HH, from which 25 studies were deemed to meet the final inclusion criteria. Twenty-four (96%) of the included studies were cohort studies. As detailed in **Table 1**, the included studies were published between 2009 and 2017. Included studies were conducted globally, with 7 studies and 3 studies conducted in India and Pakistan, respectively. The populations represented by the included studies spanned all age groups and included participants primarily from hospital settings. As the data in this review was sourced from a variety of countries, age groups and settings, the heterogeneity was considerable and/or substantial for all results. Thus, we narratively and graphically reported estimates of combined prevalence rates and the spreads of prevalence.

**Vaccine-preventable viral-induced ALF**

We narratively report the prevalence of HAV- and HBV-induced ALF by country immunization status. The point prevalence of HAV-induced ALF in countries with no routine HAV immunization at the time of data collection ranged from 2% to 81% with a combined of 27% (95% CI 13, 43), while the prevalence in countries with routine HAV immunization at the time of data collection ranged from 1% to 2% with a

combined of 2% (95% CI 1, 3) (**Figure 2**). In Argentina, the prevalence of HAV-induced ALF prior to routine immunization was approximately 50% (95% CI 45, 55), compared to approximately 1% (95% CI 0, 5) after immunization was introduced. The point prevalence of HBV-induced ALF in countries without universal HBV immunization at the time of data collection ranged from 16% to 27% with a combined of 22% (95% CI 16, 30) (**Figure 3**). The point prevalence of HBV-induced ALF in countries with universal HBV immunization at the time of data collection ranged from 0% to 83% with a combined of 20% (95% CI = 8, 35).

**ALF attributable to non-vaccine-preventable viral infections**

The point prevalence of HCV-induced ALF ranged from 2% to 25% with a combined of 9% (95% CI = 1, 21) (**Supplementary Figure 1**). The point prevalence of HEV-induced ALF ranged from 3% to 70% with a combined of 32% (95% CI 24, 41) (**Supplementary Figure 2**). The point prevalence of HDV-, HHV/HSV-, CMV-, and EBV-induced ALF were estimated to have combined prevalences of 4% (95% CI 0, 13), 6% (95% CI 1, 12), 13% (95% CI 1, 35) and 6% (95% CI 0, 24), 10% (95% CI 2, 22), 2% (95% CI 0, 5), and 1% (95% CI 0, 5), respectively (**Supplementary Figure 3**). Data was not available to estimate the burden of ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and/or HAdVs as outlined per the published protocol (11).

**Outcomes of viral-induced ALF**

The narratively reported outcomes of viral-induced ALF were found to be severe. The mortality rates associated with viral-induced ALF in lower-middle income countries ranged from 18% to 91% with a combined mortality rate of 50% (95% CI 36, 64) (**Figure 4A**). The mortality rates associated with viral-induced ALF in upper-middle income countries ranged 3% to 45% with a combined mortality rate of 26% (95% CI 1, 63) (**Figure 4A**). The mortality rates associated with viral-induced ALF in high income countries ranged from 12% to 40% with a combined mortality rate of 29% (95% CI 17, 43) (**Figure 4A**). The rate of encephalopathy associated with viral-induced ALF cases in children ranged from 69% to 100% with a combined rate of 89% (95% CI 79, 97) (**Figure 4B**). The need for liver transplantation with viral-associated ALF ranged from 4% to 62% with a combined rate of 25% (95% CI 6, 53) (**Figure 4B**). The need for renal transplant in viral-associated ALF cases ranged from 4% to 34% with a combined rate of 18% (95% CI 2, 43) (**Figure 4B**).

**Methodological quality**

Risk of bias scores were assigned by two reviewers (JP and HH) and are described in **Supplementary Table 1**. Overall, a majority of the included studies were judged as having 'low risk' of bias. Only one included study was judged as having 'moderate risk' of bias due to lack of clarity around the representativeness of the study population to the national population, methods of participant selection and methods employed to reduce the likelihood of non-response.

**Discussion**

This systematic review estimated the burden of ALF following infection with HAV, HBV, HCV, HEV, HSV/HHV, CMV, EBV, and parvo-virus B19. The prevalence of HAV-induced ALF is markedly lower in countries with routine HAV immunization while HEV was the most common etiological cause of viral-induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which seem to increase with poor economic status of the studied countries.

The estimated prevalence of HAV-induced ALF in countries with routine HAV immunization was markedly lower than the estimated prevalence in countries without routine HAV immunization. When looking at countries with data before and after the introduction of routine HAV immunization, the reduction of HAV-induced ALF due to vaccination is further highlighted. The combined prevalence of HBV-induced ALF was the same in settings with or without universal HBV immunization. Countries without universal HBV immunization programs are likely to have weak healthcare systems; thus, the reported prevalence of HBV-induced ALF is assumed to be an underestimate of the true burden in these populations due to weak routine testing and reporting systems. Currently, there is one HEV vaccine (Hecolin) licensed in China that has shown promise with a high degree of efficacy in preventing HEV genotype IV infection in healthy individuals 16 to 65 years (15). Further exploration of the efficacy of this vaccine for prevention of infection with genotypes I and II in different populations should to explore it's application in different countries and HEV endemicity settings (16).

This review estimated the mortality rate for viral-induced ALF to be approximately 50% in low- and middle- income countries (LMICs) and less than 30% in upper-middle- and high-income countries. Previous studies have estimated that mortality rates associated with ALF vary between 60% and 80%, depending on the disease etiology as well as a patient's access to care. Our review shows that although viral-induced ALF still carries a significant mortality, though possibly lower than that reported for other ALF etiologies (5, 6). Mortality data largely comes from hospitals with the capacity to diagnose viral-

induced ALF, thus deaths outside of the hospital system or ALF deaths without virological testing may not be captured in these mortality estimates. Liver transplantation is required by approximately 25% of viral-induced ALF cases and approximately 18% of viral-induced ALF cases required renal transplantation, globally. In addition to general lack of resources for transplantation, a significant proportion of potential candidates have contraindications to transplant related to poor socioeconomic status in LMICs. The transplant data included in this review may only reflect successful and unsuccessful transplants, not those that were needed but not carried out due to resource constraints or contraindications.

This review is limited by lack of data for some of the viral etiologies of ALF including for VZV, HPIVs, YFV, CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced ALF. Additionally, we believe that our findings underestimate the global burden of viral-induced ALF as some important causes of ALF (e.g. HSV/HHV) are believed to be underrecognized as they require PCR testing for diagnosis. The included studies also used varying methods of virus detection including serology and molecular tests which further added to the heterogeneity in the results of our review. This is a well-recognized limitation in studies of ALF where diagnostics are often limited by cost in under-resourced regions where viral causes of ALF are more prevalent. The limited availability of data, including lack of same country data on burden of disease before and after introduction of immunization, hindered most of the planned sub-group analyses outlined in the study protocol. Where data were available, high heterogeneity of the data led to planned meta-analyses and meta-regression analyses not being possible. Lastly, the diversity of viruses attributable to ALF cases led to low statistical power in meta-analyses conducted.

Future research should assess the burden of viral-induced ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and HAdVs. Collectively, high-quality data on all viral etiologies of ALF would allow for better pooling of results. The review team encourages future studies to incorporate health economic estimates and mathematical modelling where data permits to assist health policy decision-makers to better design strategies for the prevention and management of viral-induced ALF. Epidemiological-economic modelling of immunization against HAV, HBV and HEV may well show that introduction of vaccination could lead to future cost savings in the long run due to prevented medical care and liver failure.

**Conclusions**

We successfully addressed the aim of the study although data on VZV, HPIVs, YFV, CA16 and/or HAdVs were missing. Notwithstanding the noted limitations, it is clear that HAV, HBV and HEV – vaccine-preventable ALF etiologies – account for a large proportion of ALF (approximately 21%, 20%, 32% of viral-induced ALF cases, respectively). The burden of ALF that is associated with vaccine-preventable ALF etiologies should be used in conjunction with other available key evidence to inform practice and policies on immunization, particularly in LMICs. A majority of LMICs have established universal vaccination against HBV. The Word Health Organization has recently recommended the introduction of an HBV birth dose which is aimed at elimination of the virus and, if successful, will subsequently reduce the burden of HBV-induced ALF. Routine HAV immunization in LMICs, however, are lacking. More data is urgently needed to guide routine use of the vaccine in prevention of morbidity and mortality caused by the virus. Lastly, further applicability of HEV vaccines should be explored, especially in LMICs where resources for managing viral-induced ALF are glaringly lacking.

**Contributors**

JP, GDH, BK and RM conceived this study. JP implemented the review under the supervision of RM. JP and HSH performed the study search, screening and extraction of data under the guidance of RM. GDH and BK provided methodological expertise for this review. SS, LG, MS, and WS provided content expertise for this review and all authors will provided comments on the final manuscript before publication. JP is the guarantor of this review.

**Funding**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The Vaccines for Africa Initiative (VACFA) has funded the costs associated with the research and dissemination of the results, including publications.

**Competing interests**

None declared.

**Data availability**

All data were taken from published articles available in the public domain.

**Patient consent for publication**

Not required.

## REFERENCES


1. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology. 2017;66(5):1047-81.
2. Morabito V, Adebayo D. Fulminant Hepatitis: Definitions, Causes and Management. Health. 2014;06(10):1038-48.
3. European Association for the Study of the Liver. Electronic address eee, Clinical practice guidelines p, Wendon J, Panel m, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047-81.
4. Cervio G, Trentadue J, D'Agostino D, Luque C, Giorgi M, Armoni J, et al. Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program. Hepat Med. 2011;3:99-106.
5. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet. 2010;376(Seminar):190-201.
6. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. Systematic review: acute liver failure - one disease, more than 40 definitions. Aliment Pharmacol Ther. 2012;35(11):1245-56.
7. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012;55(3):965-7.
8. Spearman CW, McCulloch M, Millar AJ, Burger H, Numanoglu A, Goddard E, et al. Liver transplantation at Red Cross War Memorial Children's Hospital. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2006;96(9 Pt 2):960-3.
9. O'Grady JG. Acute liver failure. Postgrad Med J. 2005;81(953):148-54.
10. O'Grady J. Liver transplantation for acute liver failure. Best Pract Res Clin Gastroenterol. 2012;26(1):27-33.
11. Patterson J, Hussey HS, Abdullahi LH, Silal S, Goddard L, Setshedi M, et al. The global epidemiology of viral-induced acute liver failure: a systematic review protocol. BMJ Open. 2019.
12. Balk E, Ching M, Chen M, Trikalinos T, L KWC. Assessing the Accuracy of Google Translate to Allow Data Extraction From Trials Published in Non-English Languages. Rockville, USA: Agency for Healthcare Research and Quality; 2013 Jan 2013. Contract No.: EHC145-EF.
13. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C. Assessing risk of bias in prevalence studies: Modification of an existing tool and evidence of interrater aggreement. Journal of Clinical Epidemiology. 2012;65:934-9.
14. Werfalli M, Musekiwa A, Engel ME, Ross I, Kengne AP, Levitt NS. The prevalence of type 2 diabetes mellitus among older people in Africa: a systematic review study protocol. BMJ Open. 2014.
15. Li SW, Zhao Q, Wu T, Chen S, Zhang J, Xia NS. The development of a recombinant hepatitis E vaccine HEV 239. Hum Vaccin Immunother. 2015;11(4):908-14.
16. Wu X, Chen P, Lin H, Hao X, Liang Z. Hepatitis E virus: Current epidemiology and vaccine. Human Vaccines and Immunotherapeutics. 2016;12(10):2603-10.
17. Alam S, Azam G, Mustafa G, Azad AK, Haque I, Gani S, et al. Natural course of fulminant hepatic failure: the scenario in Bangladesh and the differences from the west. Saudi J Gastroenterol. 2009;15(4):229-33.
18. Asim M, Singla R, Gupta RK, Kar P. Clinical & molecular characterization of human TT virus in different liver diseases. Indian Journal of Medical Research. 2010;131(4):545-54.
19. Bechmann LP, Manka P, Best J, Saner FH, Paul A, Canbay A, et al. Drug-induced liver injury as predominant cause of acute liver failure in a monocenter study. Deutsche Medizinische Wochenschrift. 2014;139(17):878-82.
20. Bhatia V, Dhawan A, Arora NK, Mathur P, Das MK, Irshad M. Urinary potassium loss in children with acute liver failure and acute viral hepatitis. J Pediatr Gastroenterol Nutr. 2013;57(1):102-8.
21. Borkakoti JH, R. K.; Mohammad, A.; Kumar, A.; Kar, P. Does high viral load of hepatitis E virus influence the severity and prognosis of acute liver failure during pregnancy? Journal of Medical Virology. 2013;85(4):620-6.
22. Bravo LC, Gregorio GV, Shafi F, Bock HL, Boudville I, Liu Y, et al. Etiology, incidence and outcomes of acute hepatic failure in 0-18 year old Filipino children. Southeast Asian J Trop Med Public Health. 2012;43(3):764-72.
23. Das AK, Begum T, Kar P, Dutta A. Profile of Acute Liver Failure from North-east India and Its Differences from other Parts of the Country. Euroasian J Hepatogastroenterol. 2016;6(2):111-5.
24. Gupta P, Mittal M, Bhat NK, Agarwal RK, Gupta P, Mittal G. A hospital based retrospective study on hepatotropic viruses as a cause of acute viral hepatitis in children in Uttarakhand, India. Indian Journal of Community Health. 2015;27(4):451-5.
25. Ho CM, Lee CH, Wang JY, Lee PH, Lai HS, Hu RH. Nationwide longitudinal analysis of acute liver failure in taiwan. Medicine (Baltimore). 2014;93(4):e35.
26. Latif N, Mehmood K. Risk factors for fulminant hepatic failure and their relation with outcome in children. J Pak Med Assoc. 2010;60(3):175-8.
27. Mamun Al M, Rahman S, Khan M, Karim F. HEV infection as an aetiologic factor for acute hepatitis: experience from a tertiary hospital in Bangladesh. J Health Popul Nutr. 2009;27(1):14-9.
28. Manka P, Bechmann LP, Coombes JD, Thodou V, Schlattjan M, Kahraman A, et al. Hepatitis E Virus Infection as a Possible Cause of Acute Liver Failure in Europe. Clin Gastroenterol Hepatol. 2015;13(10):1836-42.e2; quiz e157-8.
29. Mendizabal MM, S.; Videla, M. G.; Anders, M.; Zerega, A.; Balderramo, D. C.; Chan, D.; Barrabino, M.; Gil, O.; Mastai, R.; Yantorno, S.; Gadano, A.; Silva, M. O. Changing etiologies and outcomes of acute liver failure: Perspectives from 6 transplant centers in Argentina. Liver Transplantation. 2014;20(4):483-9.
30. Mishra SB, J.; Kumar, S.; Kar, P. Role of HEV antigen detection in HEV-related acute viral hepatitis and acute liver failure. Journal of Medical Virology. 2016;88(12):2179-85.
31. Mumtaz K, Azam Z, Hamid S, Abid S, Memon S, Ali Shah H, et al. Role of N-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. Hepatology International. 2009;3(4):563-70.
32. Pandit A, Mathew LG, Bavdekar A, Mehta S, Ramakrishnan G, Datta S, et al. Hepatotropic viruses as etiological agents of acute liver failure and related-outcomes among children in India: a retrospective hospital-based study. BMC Res Notes. 2015;8:381.

33. Poovorawan Y, Chongsrisawat V, Shafi F, Boudville I, Liu Y, Hutagalung Y, et al. Acute hepatic failure among hospitalized Thai children. Southeast Asian J Trop Med Public Health. 2013;44(1):50-3.
34. Schwarz KBO, Dominic Dell; Lobritto, Steven J.; Lopez, M. James; Rodriguez-Baez, Norberto; Yazigi, Nada A.; Belle, Steven H.; Zhang, Song; Squires, Robert H.; for the Pediatric Acute Liver Failure Study, Group. Analysis of Viral Testing in Nonacetaminophen Pediatric Acute Liver Failure. Journal of Pediatric Gastroenterology & Nutrition. 2014;59(5):616-23.
35. Shalimar, Kedia S, Gunjan D, Sonika U, Mahapatra SJ, Nayak B, et al. Acute Liver Failure Due to Hepatitis E Virus Infection Is Associated with Better Survival than Other Etiologies in Indian Patients. Dig Dis Sci. 2017;62(4):1058-66.
36. Silverio CE, Smithen-Romany CY, Hondal NI, Diaz HO, Castellanos MI, Sosa O. Acute liver failure in Cuban children. MEDICC Rev. 2015;17(1):48-54.
37. Somasekar SL, D.; Rule, J.; Naccache, S. N.; Stone, M.; Busch, M. P.; S.; ers, C.; Lee, W. M.; Chiu, C. Y. Viral Surveillance in Serum Samples from Patients with Acute Liver Failure by Metagenomic Next-Generation Sequencing. Clinical Infectious Diseases. 2017;65(9):1477-85.
38. Uddin Jamro BMC, S.; Mal Makheja, P.; Ahmed Soomro, A. Etiology, outcome and risk factors for fulminant hepatic failure in children at a tertiary care hospital, Sukkur, Pakistan. Rawal Medical Journal. 2013;38(3):219-22.
39. Tsunoda T, Inui A, Iwasawa K, Oikawa M, Sogo T, Komatsu H, et al. Acute liver dysfunction not resulting from hepatitis virus in immunocompetent children. Pediatr Int. 2017;59(5):551-6.
40. Zhao P, Wang CY, Liu WW, Wang X, Yu LM, Sun YR. Acute liver failure in Chinese children: a multicenter investigation. Hepatobiliary Pancreat Dis Int. 2014;13(3):276-80.

**FIGURE LEDENDS**

Figure 1
PRISMA Flow Diagram describing selection of studies.

Figure 2
Abbreviations: HAV = hepatitis A virus, ALF = acute liver failure, CI = confidence interval, I2 = heterogeneity statistic

Figure 3
Abbreviations: HBV = hepatitis B virus, ALF = acute liver failure, CI = confidence interval, I2 = heterogeneity statistic

Figure 4
Abbreviations: ALF = acute liver failure, CI = confidence interval, I2=heterogeneity statistic, NA = not applicable

## TABLES

**Table 1: Characteristics of included studies**

| Study | Study Design | Aim | Country | Income Level | Start of Data Collection | End of Data Collection | ALF Case Definition |
|---|---|---|---|---|---|---|---|
| Alam et al., 2009 (17) | Prospective cohort | To evaluate the etiology, complications, and outcome of FHF | Bangladesh | Lower-middle | 3-Nov | 8-May | Occurrence of hepatic encephalopathy within 8 weeks of onset of jaundice in patients with no previous liver disease and the presence of coagulopathy as proved by a PT > 15 s or INR > 1.5 |
| Asim et al., 2009 (18) | Cross-sectional | To analyze serum samples from patients with ALF for hepatitis A-G viral markers | India | Lower-middle | 1-Jun | 4-May | Patient become deeply jaundiced and went into hepatic encephalopathy within 8 weeks of onset of the disease, with no past history of chronic hepatitis |
| Bechmann et al., 2014 (19) | Retrospective cohort | To identify currently predominant etiologies of ALF at a transplant center | Germany | High | 1-Jan | 12-Feb | *Acute Liver Failure Study Group Germany* case definition: INR > 1.5 and encephalopathy of any grade. Pre-existing liver disease and systemic cause of liver failure were excluded |
| Bhatia et al., 2013 (20) | Prospective cohort | To analyze clinical features, liver function tests, hepatitis viral markers and clinical outcomes in patients with ALF | India | Lower-middle | Jun-99 | 1-Jan | Development of hepatic encephalopathy within 26 weeks of the first symptoms of acute hepatitis-like illness without any history of underlying liver disease |
| Borkakoti et al., 2013 (21) | Prospective cohort | To determine the viral load of HEV and its association with the disease severity in patients with ALF in comparison with patients with ALF due to other hepatides | India | Lower-middle | 6-Jan | 11-Dec | Development of encephalopathy within 8 weeks of the onset of jaundice without any past history of chronic liver disease; diagnosed as a self-limiting disease and a serum aspartate aminotransferase elevation of at least fivefold or clinical jaundice or both |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Bravo et al., 2012 (22) | Prospective & retrospective cohort | To investigate the etiology, outcomes and incidence of AHF among children 0-18 years old | Philippines | Lower-middle | Jan-00 | 6-Dec | Onset of coagulopathy and/or encephalopathy ≤4 weeks after the onset of symptoms, a prothrombin time > 2, an increased bilirubin and evidence for liver failure complicated by encephalopathy |
| Cervio et al., 2011 (4) | Retrospective cohort | To investigate the impact of HAV UI on the trends in the occurrence of FHF in children | Argentina | High | Mar-93 | 5-Jul | *Mieli-Vergani* case definition: a multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in a patient with or without recognized underlying chronic liver disease (**Cheeseman & Mieli-Vergani, 2004**) |
| Das et al., 2016 (23) | Prospective cohort | To determine the profile of ALF etiologies | India | Lower-middle | 7-Jan | 15-Dec | History of development of encephalopathy within 8 weeks of disease onset |
| Gupta et al., 2015 (24) | Retrospective cohort | To determine the profile of Hepatitis A, B, C and E as a cause of AHF in children in a tertiary care hospital | India | Lower-middle | 11-Jan | 14-Dec | Elevated ALT levels or AST of at least five-fold with clinical jaundice and without evidence of chronic liver disease. Patients who had INR > 1.5 with encephalopathy or INR > 2 without encephalopathy |
| Ho et al., 2014 (25) | Prospective cohort | To investigate the incidence, etiology, outcomes, and prognostic factors of ALF | Taiwan | High income | 5-Jan | 7-Sep | International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 570.0 |
| Latif et al., 2010 (26) | Prospective cohort | To identify the risk factors for FHF and their relationship with the outcome in children | Pakistan | Lower-middle | 6-Sep | 7-Feb | Development of encephalopathy within 8 weeks of the onset of jaundice having evidence of coagulopathy i.e. PT deranges > 4 s of control and deranged liver function i.e. TSB > 1.5 mg/dl, AT > 40 IU/L |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mamun et al., 2009 (27) | Retrospective cohort | To assess the burden of HEV as a cause of ALF | Bangladesh | Lower-middle | 4-Jun | 6-Dec | Previously healthy patients who presented with severe impairment of hepato-cellular function, i.e. encephalopathy, coagulopathy, and jaundice, within six months of onset of symptoms |
| Manka et al., 2015 (28) | Retrospective cohort | To investigate the causes of previously diagnosed indeterminate cases ALF | Germany | High | 6-Nov | 13-Dec | Significant liver dysfunction with pathologically increased laboratory parameters [AST, ALT, AP], an existing coagulopathy in terms of an INR > 1.5, and with the concomitant presence of any degree of encephalopathy |
| Mendizabal et al., 2014 (29) | Retrospective cohort | To determine the causes and short-term outcomes of ALF | Argentina | High | 5-Jun | 11-Dec | Presence of coagulopathy [INR > 1.5 or prothrombin index < 50%] and any grade of HE within 26 weeks of the first symptoms without a known underlying liver disease |
| Mishra et al., 2016 (30) | Retrospective cohort | To assess the relative efficacy of HEV antigen detection by ELISA in patients with ALF | India | Lower-middle | 13-Nov | 15-Jan | Any evidence of coagulation abnormality, generally INR >1.5 and any degree of mental alteration (encephalopathy) without pre-existing cirrhosis and with an illness of < 4 weeks duration |
| Mumtaz et al., 2009 (31) | Prospective cohort compared to historical control | To assess the etiology, prothrombin time (PT), alanine aminotransferase, creatinine, albumin for non-acetaminophen-induced ALF | Pakistan | Lower middle | Jan-00 | 7-Mar | Rapid development of acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver |
| Pandit et al., 2015 (32) | Retrospective cohort | To assess the frequency of hepatotropic viruses as etiological agents of ALF | India | Lower-middle | 3-Jan | 5-Dec | Onset of encephalopathy ≤28 days after the onset of symptoms with INR > 2 and increased bilirubin complicated by encephalopathy in patients |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | without a previous history of liver disease |
| Poovorawan (33) et al., 2013 | Prospective cohort | To determine the causes and outcomes of Thai children with AHF | Thailand | Upper-middle | 2-Jan | 5-Sep | *International Association for the Study of the Liver* case definition: **(Tandon et al, 1999)** |
| Schwarz et al., 2014 (34) | Retrospective cohort - Patient registry | To analyzed results of viral testing among non-acetaminophen ALF study participants | USA/Canada/UK | High | Dec-99 | 12-Dec | No known evidence of chronic liver disease, with evidence of acute liver injury, and hepatic-based coagulopathy not corrected by vitamin K with the follow parameters: PT ≥ 15 s or INR ≥ 1.5 in the presence of clinical HE or a PT ≥ 20 s or INR ≥ 2.0 regardless of the presence or absence of clinical HE |
| Shalimar et al., 2017 (35) | Retrospective cohort | To assess the differences in the course of HEV-ALF as compared to other etiologies of ALF | India | Lower middle | Jan-86 | 15-Dec | *International Association for the Study of Liver* (IASL) case definition: Occurrence of encephalopathy within 4 weeks from the onset of symptoms in the absence of preexisting liver disease |
| Silverio et al., 2015 (36) | Retrospective cohort | To describe the clinical features of children treated for ALF | Cuba | Upper-middle | 5-Jan | 11-Dec | Evidence of liver damage in the absence of prior known chronic liver disease; altered coagulation, expressed as PT >15 s with encephalopathy; or PT > 20 s with or without encephalopathy—all this within eight weeks of onset of clinical symptoms |
| Somasekar et al., 2017 (37) | Retrospective cohort | To investigate the causes of previously diagnosed indeterminate cases ALF | United States | High | Jan-98 | 10-Dec | *United States Acute Liver Failure Study Group* case definition |
| Uddin Jamro et al., 2013 (38) | Retrospective cohort | To study the etiology, outcome and risk factors for FHF in children at | Pakistan | Lower-middle | 7-Jul | 12-Jun | Presence of acute liver failure (coagulopathy PT > 20 s or INR > 2), HE without pre-existing liver disease, within 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | a tertiary care hospital | | | | | weeks of the onset of clinical liver disease |
| Tsunoda et al., 2017 (39) | Prospective cohort | To identify the roles of CMV, EBV and HHV in immunocompetent children with acute liver failure not resulting from hepatitis virus | Japan | High | 7-Jan | 13-Dec | Liver dysfunction with elevated AST and ALT > 30 IU/L |
| Zhao et al., 2014 (40) | Retrospective cohort | To investigate etiologies and outcomes of children with ALF | China | Middle | 7-Jan | 12-Dec | Coagulopathy [PTA ≤40% or INR ≥ 1.5 excluding hematologic diseases] and jaundice [Tbil ≥ 171 μmol/L] within 4 weeks in a child without pre-existing liver diseases |

**Abbreviations:** ALF = acute liver failure; FHF = fulminant hepatic failure; AHF = acute hepatic failure; HEV = hepatitis E virus; CMV = cytomegalovirus; EBV = Epstein Barr virus; HHV = human herpesvirus; ELISA = enzyme-linked immunosorbent assay; INR = international normalized ratio; PT = prothrombin time; s = second; TSB = total serum bilirubin; HE = hepatic encephalopathy; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP = alkaline phosphatase; PTA = plasma thromboplastin antecedent

Figure 1: Flow diagram for selection of studies

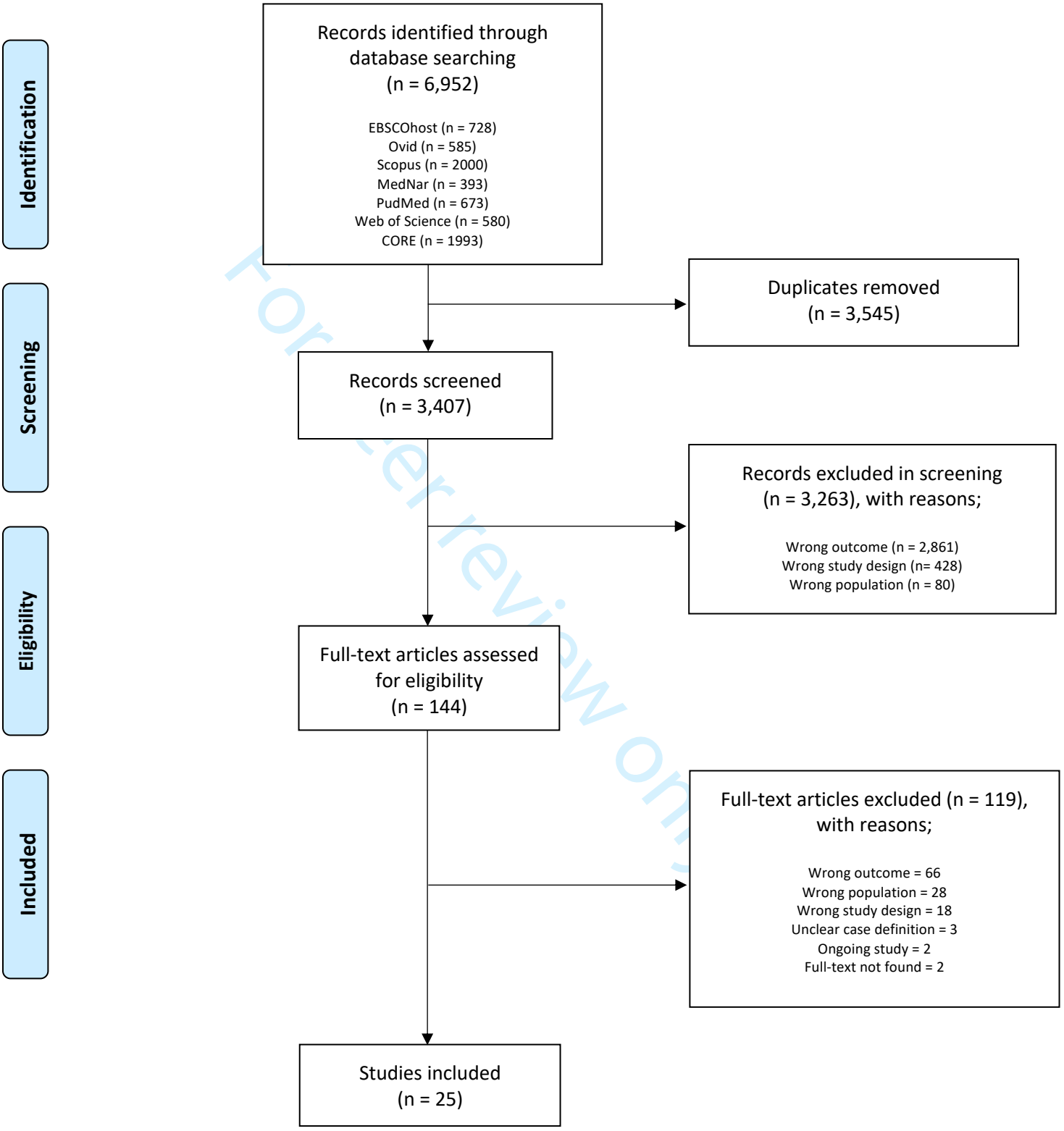


Figure 2: Prevalence of HAV-induced ALF by country HAV immunization status

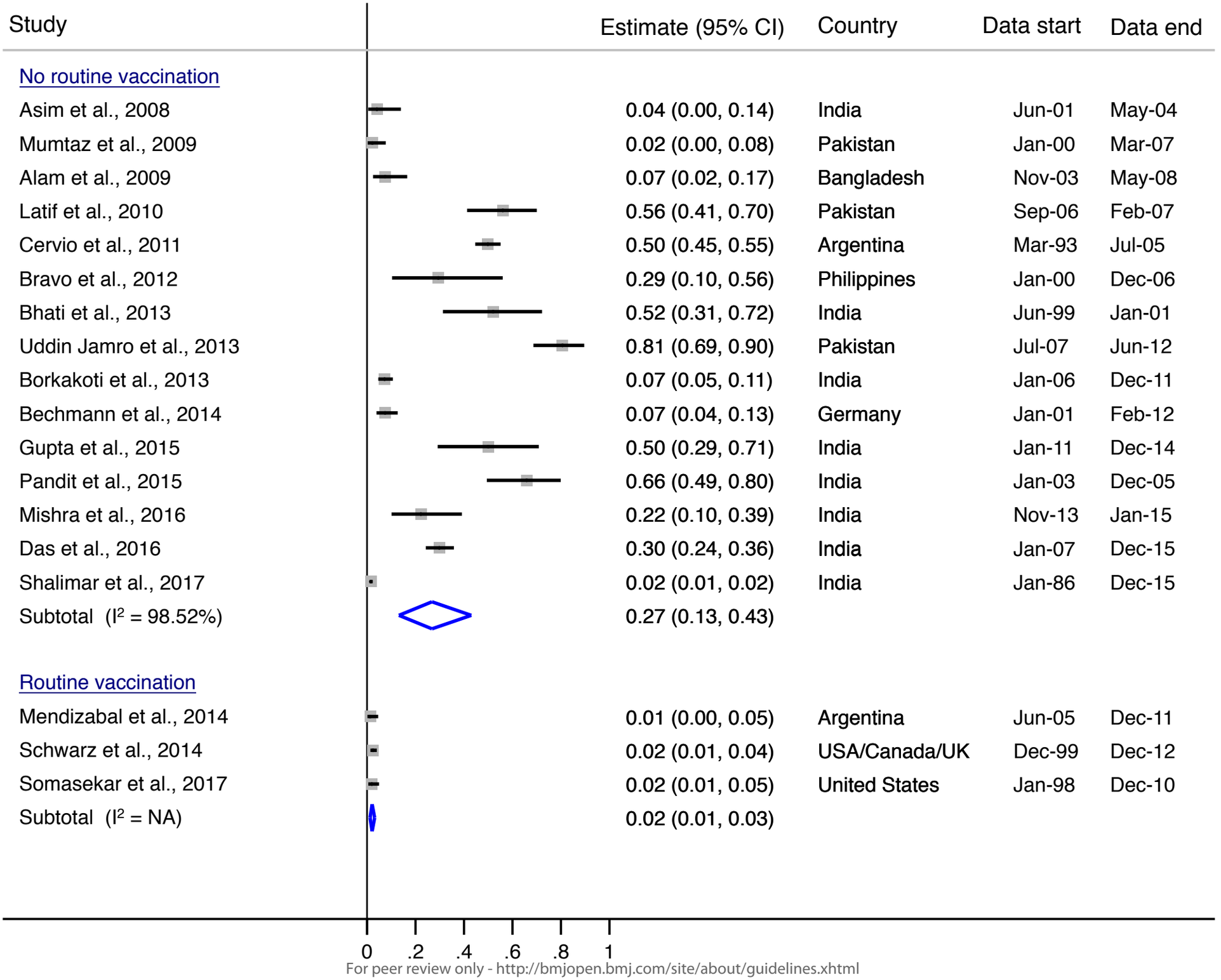
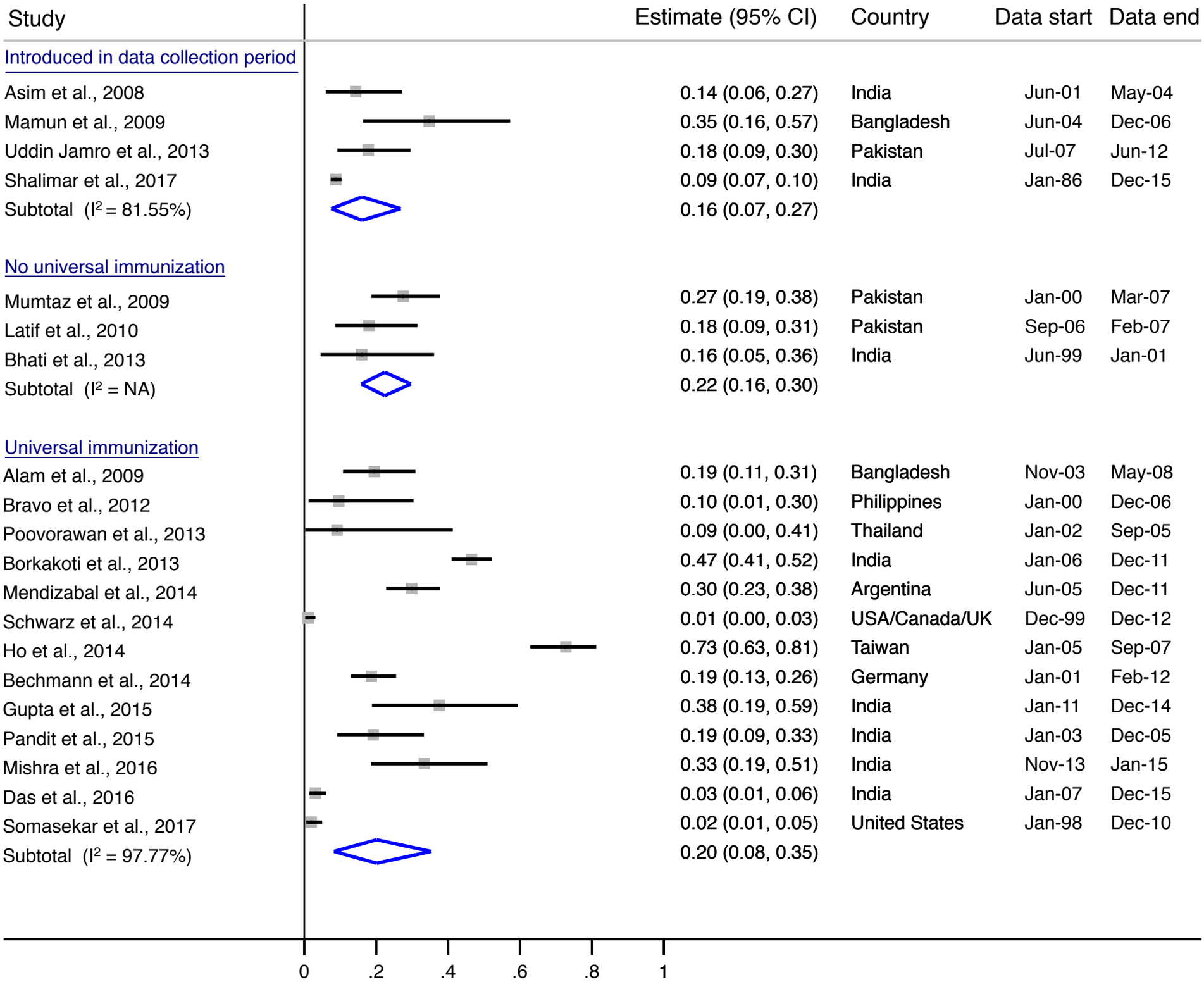
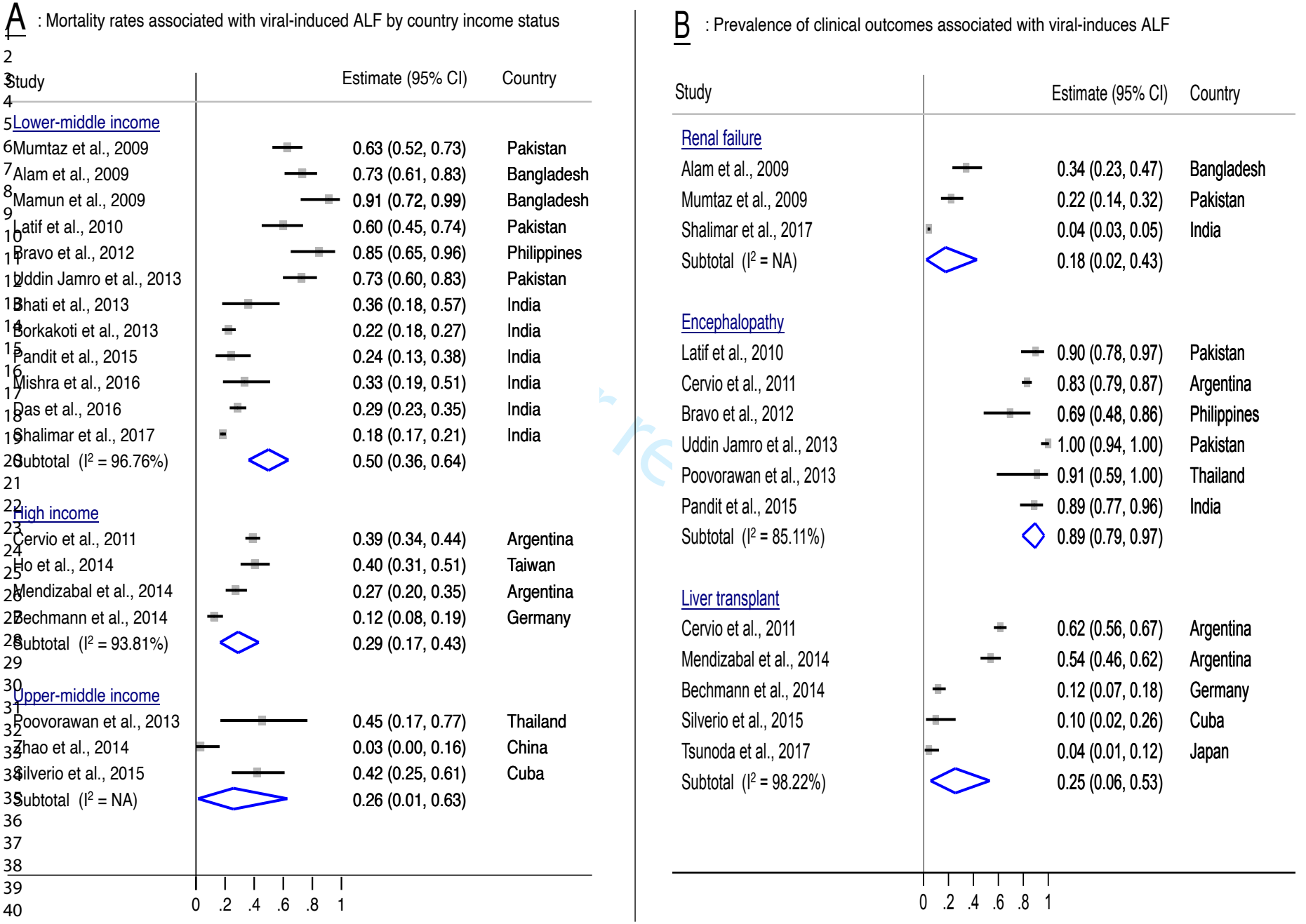


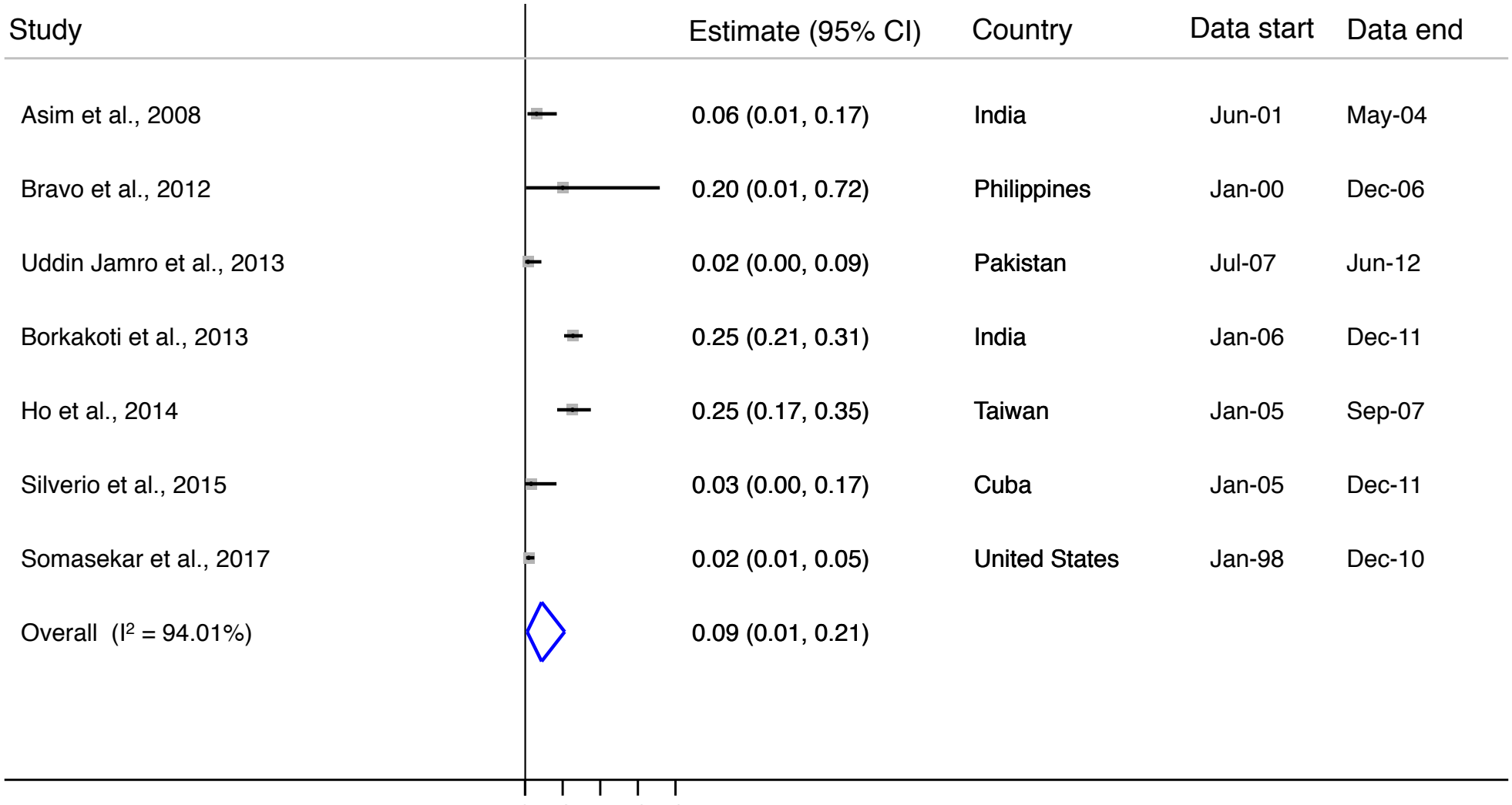
Figure 3: Prevalence of HBV-induced ALF by country HBV immunization status



# Figure 4: Prevalence of outcomes associated with viral-induced ALF



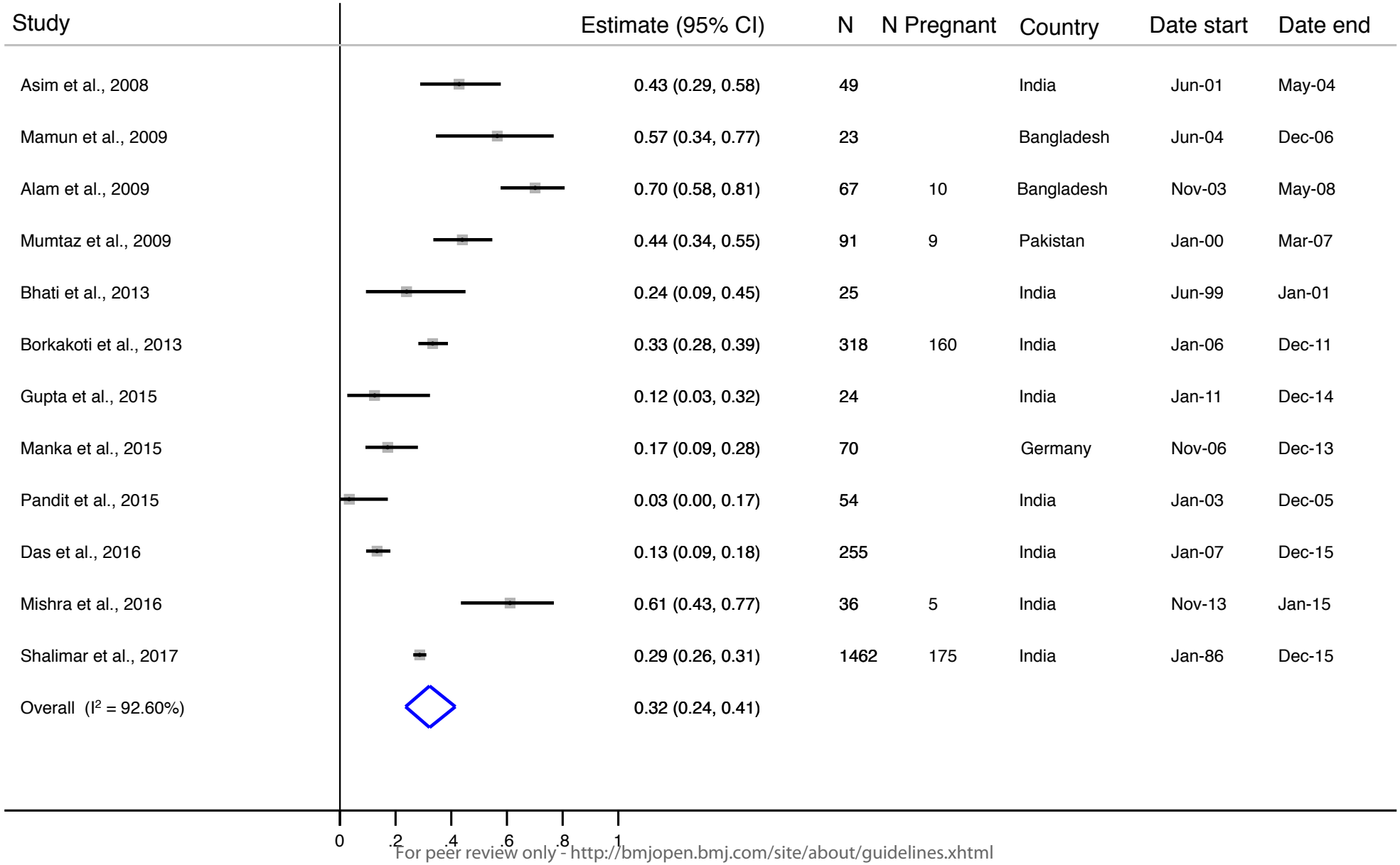
# Supplementary Figure 1: Prevalence of HCV-induced ALF






Abbreviations: HCV = hepatitis C virus, ALF = acute liver failure, CI = confidence interval, $I^2$ = heterogeneity statistic

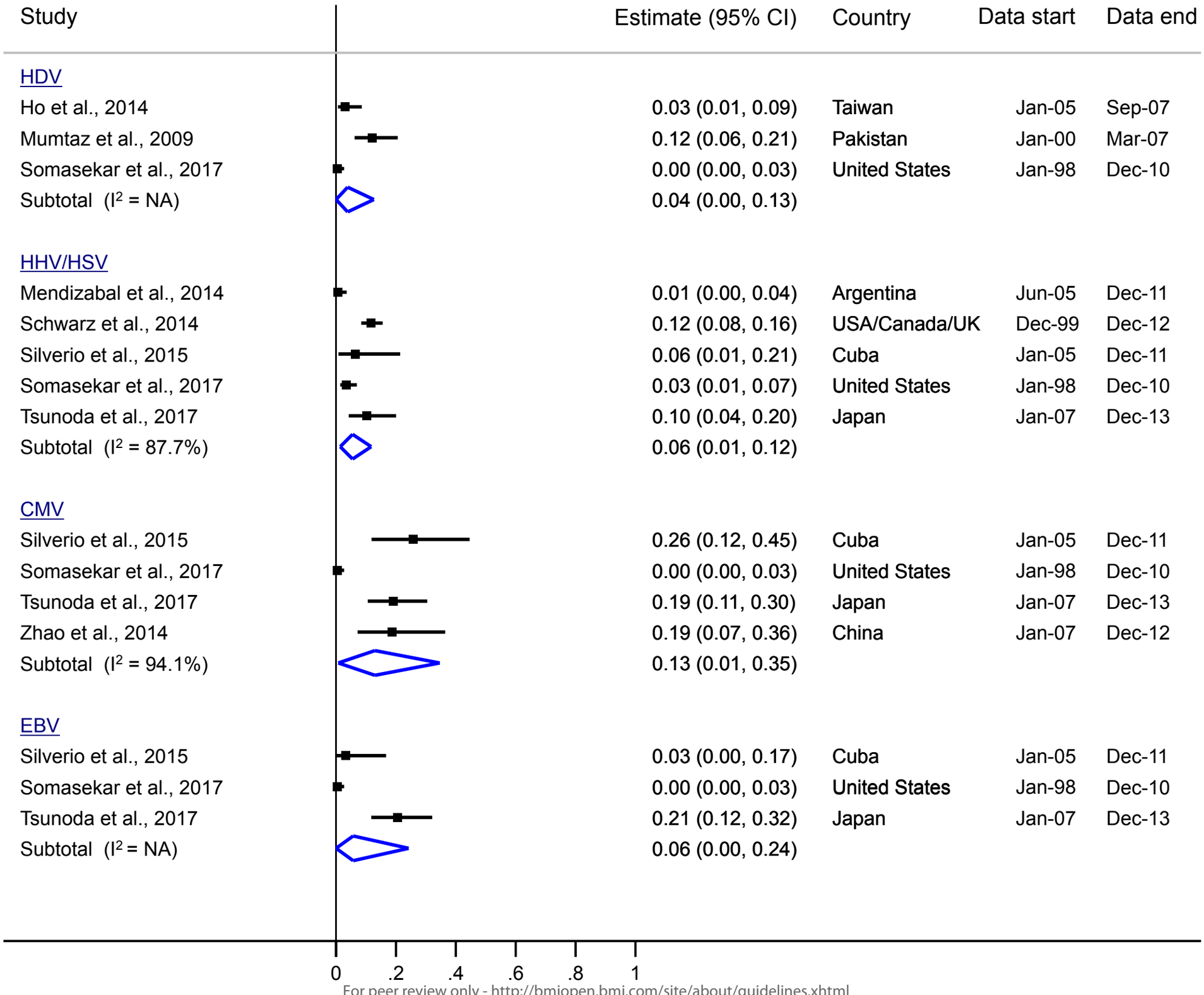
# Supplementary Figure 2: Prevalence of HEV-induced ALF






Abbreviations: HEV = hepatitis E virus, ALF = acute liver failure, CI = confidence interval, $I^2$ = heterogeneity statistic

# Supplementary Figure 3: Prevalence of HDV-, HHV/HSV-, CMV- and EBV-induced AFL






Abbreviations: HDV = hepatitis D virus, HHV/HSV = Human Herpes virus/Herpes Simplex Virus, CMV = Cytomegalovirus, EBV = Epstein-Barr virus,

## SUPPLEMENTARY TABLE

**Supplementary Table 1: Risk of bias judgements for included studies**

| Study ID | Representation of the national population | Representation of target population | Random selection or census | Minimal likelihood of non-response bias | Data collected directly from participants | Acceptable case definition | Valid measurement | Same mode of data collection | Appropriate length | Appropriate numerator(s) and denominator(s) | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alam et al., 2009 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Asim et al., 2009 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Bechmann et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Bhati et al., 2013 | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Borkakoti et al., 2013 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Bravo et al., 2012 | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Cervio et al., 2011 | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Das et al., 2016 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Gupta et al., 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Ho et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Latif et al., 2010 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Mamun et al., 2009 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Manka et al., 2015 | No | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | 8 |
| Mendizabal et al., 2014 | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Mishra et al., 2016 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 7 |
| Mumtaz et al., 2009 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Pandit et al., 2015 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Poovorawan et al., 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 9 |
| Schwarz et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 9 |
| Shalimar et al., 2017 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Silverio et al., 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Somasekar et al., 2017 | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Uddin Jamro et al., 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Tsunoda et al., 2017 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Zhao et al., 2014 | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |

# PRISMA 2009 Checklist

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

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 4 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 4-5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 4 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 5 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 6 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 5-6 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 5-6 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 5-6 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 6-8 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 8 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 10 |

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

# PRISMA 2009 Checklist

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

BMJ Open

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

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-037473.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 04-Jun-2020 |
| Complete List of Authors: | Patterson, Jenna; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Hussey, Hannah; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health & Family Medicine<br>Silal, Sheetal; University of Cape Town, Department of Statistical Sciences; University of Oxford, Nuffield Department of Medicine<br>Goddard, Liz; University of Cape Town, Department of Paediatrics, Red Cross War Memorial Children's Hospital<br>Setshedi, Mashiko; University of Cape Town, Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital<br>Spearman, Wendy ; University of Cape Town, Department of Medicine, Division of Hepatology, Groote Schuur Hospital<br>Hussey, Gregory; University of Cape Town Faculty of Health Sciences, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Kagina, Benjamin; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine<br>Muloiwa, Rudzani; University of Cape Town, 5Department of Pediatrics & Child Health, Red Cross War Memorial Children's Hospital; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiaitve, School of Public Health and Family Medicine |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Infectious diseases |
| Keywords: | Epidemiology < INFECTIOUS DISEASES, Hepatology < INTERNAL MEDICINE, VIROLOGY |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

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

Jenna Patterson[1,2], Hannah Sophia Hussey[1,2], Sheetal Silal[3,4], Liz Goddard[5], Mashiko Setshedi[6], C. Wendy Spearman[7], Gregory D. Hussey[1,8] Benjamin M. Kagina[1,2] and Rudzani Muloiwa[1,5]

[1]Vaccines for Africa Initiative, University of Cape Town, South Africa

[2]School of Public Health & Family Medicine, University of Cape Town, South Africa

[3]Modelling and Simulation Hub, Africa, Department of Statistical Sciences, Faculty of Science, University of Cape Town, South Africa

[4]Nuffield Department of Medicine, Oxford University, Oxford, United Kingdom

[5]Department of Pediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town

[6]Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital, University of Cape Town, South Africa

[7]Division of Hepatology, Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital, South Africa

[8]Institute of Infectious Disease and Molecular Medicine, University of Cape Town, South Africa

[5]Department of Pediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town

*Corresponding author*: Jenna Patterson

*Corresponding author's ORCID iD:* 0000-0002-3927-037X

*Corresponding author's email address*: pttjen005@myuct.ac.za

*Corresponding author's postal address:* Vaccines for Africa Initiative, Room N2.09A, Werner Beit North, Health Sciences Campus, Anzio Road, Observatory, 7925

*H.S. Hussey email address:* hshussey@gmail.com

*S. Silal email address:* sheetal.silal@uct.ac.za

*E. Goddard email address:* liz.goddard@uct.ac.za

*M. Setshedi email address:* mashiko.setshedi@uct.ac.za

*W. Spearman email address:* wendy.spearman@uct.ac.za

*G.D. Hussey email address:* gregory.hussey@uct.ac.za

*B.M. Kagina email address:* benjamin.kagina@uct.ac.za

*R. Muloiwa email address:* rudzani.muloiwa@uct.ac.za

## REQUIRED STATEMENTS

### Conflict of interest disclosure

All authors have no conflicts of interest to declare.

### Ethics approval statement

This study did not require ethics approval as it uses publicly available, published data.

### Patient consent statement

This study did not require consent from patients as it uses no individual data.

### Permission to reproduce material from other sources

This study has cited all references which are published and publicly available.

## ABBREVIATIONS

- Acute liver failure (ALF)
- 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)
- Human parainfluenza viruses (HPIVs)
- Yellow fever virus (YFV)
- Human herpesvirus 6 (HHV-6)
- Cytomegalovirus (CMV)
- Coxsackievirus (CA16)
- Adenovirus (HAdVs)
- Medical Subject Headings (MESH)
- Low- and middle- income countries (LMICs)

## ABSTRACT

**Objectives:** The etiology and burden of viral-induced acute liver failure (ALF) remains unclear, globally. It is important to understand the epidemiology of viral-induced ALF to plan for clinical case management and case prevention.

**Participants:** This systematic review was conducted to synthesize data on the relative contribution of different viruses to the etiology of viral-induced ALF in attempt to compile evidence that is currently missing in the field. EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science were searched for relevant literature published from 2009 to 2019. The initial search was run on 9 April 2019 and updated via PubMed on 30 September 2019 with no new eligible studies to include. Twenty-five eligible studies were included in the results of this review.

**Results:** This systematic review estimated the burden of acute liver failure following infection with HBV, HAV, HBV, HCV, HEV, HSV/HHV, CMV, EBV, and parvo-virus B19. Data were largely missing for ALF following infection with VZV, HPIVs, YFV, CA16 and/or HAdVs. The prevalence of HAV-induced ALF was markedly lower in countries with routine HAV immunization vs no routine HAV immunization. Hepatitis E virus was the most common etiological cause of viral-induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which appear to increase with poor economic status of the studied countries.

**Conclusions:** Immunization against HAV and HBV should be prioritized in LMICs to prevent high viral-induced ALF mortality rates, especially in settings where resources for managing acute liver failure are lacking. The expanded use of HEV immunization should be explored as HEV was the most common cause of ALF.

**Registration:** PROSPERO registration number CRD42017079730


**Strengths and limitations**

- Comprehensive and exhaustive search for relevant studies from several databases.
- Comprehensive diagnostic inclusion criteria for acute liver failure cases according to international guideline.
- Lack of language restrictions in search lead to inclusion of geographically diverse data.
- Findings are limited by lack of data for some of the viral etiologies of ALF which may have led to an underestimation of the global burden of viral-induced ALF.
- Diversity of viruses attributable to ALF cases and viral detection methods led to high heterogeneity and low statistical power in meta-analyses conducted.

**MANUSCRIPT**

## Background

Acute liver failure (ALF) refers to the development of encephalopathy and synthetic function impairment following acute liver injury in an individual without pre-existing liver disease (1). The presence of encephalopathy is not required to define ALF in paediatrics, but is an essential component of the definition in adults (1). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver diseases, vascular causes and/or malignancies. Acute viral hepatitis has been identified as the most common cause of ALF among all ages in Asia and Africa and one of the most common causes of ALF in children in Asia and South America (2, 3). The incidence of viral-induced ALF has substantially declined in Europe following the introduction of universal immunization against the hepatitis B virus (HBV), with only 19% of all ALF cases now attributable to viral infection in the European population (4). The introduction of routine immunization against the hepatitis A virus (HAV) in Argentina has reduced the number of hepatitis A induced ALF cases by more than 25% (4).

Fatality rates associated with ALF vary between 60% and 80%, depending on the disease etiology as well as a patient's access to care (5, 6). 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 (7). A large proportion of patients with ALF in both high and low resource settings, however, are deemed to have contraindications to transplantation or deteriorate beyond transplantation before a liver donor is found (8-10).

The burden of viral-induced ALF around the world still remains unclear, with little to no data collected regarding the disease incidence (3). Establishing the etiology of viral-induced ALF is important for early initiation of treatment, determining the prognosis of the liver failure and identifying potential contraindications to liver transplantation. Most importantly, understanding the epidemiology of vaccine-preventable etiologies of ALF should be prioritised in under-resourced regions with limited access to facilities for transplantation. This review aims to synthesize data on the relative contribution of different viruses to the etiology of viral-induced ALF in attempt to compile evidence that is currently missing in the field.

*Bernal et al. 2010* completed a review of the burden of acute and fulminant liver failure based on literature published between 1997 and 2009. The review became the bases for guidelines for clinical

practice (5). In this systematic review, we assess whether data have changed following the Bernal publication, and whether there is evidence to warrant a review of clinical practice.

**Objectives**

- To estimate the prevalence of 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), coxsackievirus (CA16) and/or adenovirus (HAdVs) among patients with ALF.
- To estimate the mortality rate for cases of 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
- To estimate the prevalence and incidence of liver transplantation for cases of 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

## Methods

This systematic review was registered with PROSPERO (registration number CRD42017079730) and the methods for its conduction have been published (11). The results of the review are reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines checklist.

**Study eligibility criteria**

Published cross-sectional, surveillance and cohort studies reporting the outcomes of interest in patients with 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 were eligible for inclusion in this study. Studies were eligible for inclusion if they had clearly stated case definitions of viral-induced ALF and confirmed ALF cases using both clinical and serological, molecular or culture diagnostic methods.

**Search strategy**

A combination of the following search terms (including the use of Medical Subject Headings (MESH)) was used and adapted for each of the relevant electronic databases: 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), coxsackie virus and adenovirus.

The following electronic databases were searched for relevant literature published from 2009 to 2019: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The search was run on 9 April 2019 and updated via PubMed on 30 September 2019 with no new eligible studies to include.

**Data extraction**

Study characteristics and outcomes of interests were extracted from the included studies on a pre-designed data extraction form by two independent reviewers (JP and HH). Prior to use by the two reviewers, the reliability of the extraction form was assessed by piloting 10 randomly selected articles that met the inclusion criteria. The study team resolved any disagreements in data extraction through consensus in consultation with RM. In cases where studies were in German, HH provided translation. In cases where studies were not available in English or German, google translate was used to translate the article to English (12).

**Data synthesis and analysis**

A random-effects model was fitted to the study data as it included data taken from a series of independently performed studies in different populations. We assessed heterogeneity by calculating $I^2$ statistics (threshold $I^2 > 40\%$). The values of $I^2$ were categorized for heterogeneity as follows: “not important” ($\leq$ 40%), “moderate” ($>$ 40% to $\leq$ 60%) and “considerable” ($>$ 60% to $\leq$ 80%) and “substantial” ($>$ 80% to $\leq$ 100%). Where “not important” or “moderate” heterogeneity existed between studies ($I^2 \leq 60\%$), pooled outcome measures were reported with 95% confidence intervals for each respective outcome. Where “considerable” or “substantial” heterogeneity exists between studies ($I^2 > 60\%$), forest plots and prevalence ranges calculated using the random-effects model were used to narratively describe each outcome.

**Risk of bias assessment**

Each included study was assessed for risk of bias and quality using the Hoy *et al.,* 2012 tool for observational studies (13, 14). Studies were judged as having 'low risk' if scored 8-10, 'moderate risk' if scored 5-7 and 'high risk' if scored 0-5. All risk of bias judgements were made by both JP and HH. In case of disagreement in risk of bias and quality assessment, a final decision was made through consensus in consultation with RM.

**Patient and public involvement**

This review 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 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 was required; however, it is hoped that the findings of this review will help to highlight the burden that ALF places on populations without routine vaccination.

## Results

The initial database searches yielded 6,952 records, from which 3,545 duplicates were removed. A further 3,263 were excluded following the screening of titles and abstracts (**Figure 1**). The full text of the remaining 144 records were screened by JP and HH, from which 25 studies were deemed to meet the final inclusion criteria. Twenty-four (96%) of the included studies were cohort studies. As detailed in **Table 1**, the included studies were published between 2009 and 2017. Included studies were conducted globally, with 7 studies and 3 studies conducted in India and Pakistan, respectively. The populations represented by the included studies spanned all age groups and included participants primarily from hospital settings. As the data in this review was sourced from a variety of countries, age groups and settings, the heterogeneity was considerable and/or substantial for all results. Thus, we narratively and graphically reported estimates of combined prevalence rates and the spreads of prevalence.

**Vaccine-preventable viral-induced ALF**

We narratively report the prevalence of HAV- and HBV-induced ALF by country immunization status. The point prevalence of HAV-induced ALF in countries with no routine HAV immunization at the time of data collection ranged from 2% to 81% with a combined of 27% (95% CI 13, 43), while the prevalence in countries with routine HAV immunization at the time of data collection ranged from 1% to 2% with a combined of 2% (95% CI 1, 3) (**Figure 2**). In Argentina, the prevalence of HAV-induced ALF prior to

routine immunization was approximately 50% (95% CI 45, 55), compared to approximately 1% (95% CI 0, 5) after immunization was introduced. The point prevalence of HBV-induced ALF in countries without universal HBV immunization at the time of data collection ranged from 16% to 27% with a combined of 22% (95% CI 16, 30) (**Figure 3**). The point prevalence of HBV-induced ALF in countries with universal HBV immunization at the time of data collection ranged from 0% to 83% with a combined of 20% (95% CI = 8, 35).

**ALF attributable to non-vaccine-preventable viral infections**

The point prevalence of HCV-induced ALF ranged from 2% to 25% with a combined of 9% (95% CI = 1, 21) (**Supplementary Figure 1**). The point prevalence of HEV-induced ALF ranged from 3% to 70% with a combined of 32% (95% CI 24, 41) (**Supplementary Figure 2**). The point prevalence of HDV-, HHV/HSV-, CMV-, and EBV-induced ALF were estimated to have combined prevalences of 4% (95% CI 0, 13), 6% (95% CI 1, 12), 13% (95% CI 1, 35) and 6% (95% CI 0, 24), 10% (95% CI 2, 22), 2% (95% CI 0, 5), and 1% (95% CI 0, 5), respectively (**Supplementary Figure 3**). Data was not available to estimate the burden of ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and/or HAdVs as outlined per the published protocol (11).

**Outcomes of viral-induced ALF**

The narratively reported outcomes of viral-induced ALF were found to be severe. The mortality rates associated with viral-induced ALF in lower-middle income countries ranged from 18% to 91% with a combined mortality rate of 50% (95% CI 36, 64) (**Figure 4A**). The mortality rates associated with viral-induced ALF in upper-middle income countries ranged 3% to 45% with a combined mortality rate of 26% (95% CI 1, 63) (**Figure 4A**). The mortality rates associated with viral-induced ALF in high income countries ranged from 12% to 40% with a combined mortality rate of 29% (95% CI 17, 43) (**Figure 4A**). The rate of encephalopathy associated with viral-induced ALF cases in children ranged from 69% to 100% with a combined rate of 89% (95% CI 79, 97) (**Figure 4B**). The need for liver transplantation with viral-associated ALF ranged from 4% to 62% with a combined rate of 25% (95% CI 6, 53) (**Figure 4B**). The need for renal transplant in viral-associated ALF cases ranged from 4% to 34% with a combined rate of 18% (95% CI 2, 43) (**Figure 4B**).

**Methodological quality**

Risk of bias scores were assigned by two reviewers (JP and HH) and are described in **Supplementary Table 1**. Overall, a majority of the included studies were judged as having 'low risk' of bias. Only one included study was judged as having 'moderate risk' of bias due to lack of clarity around the representativeness of the study population to the national population, methods of participant selection and methods employed to reduce the likelihood of non-response.

**Discussion**

This systematic review estimated the burden of ALF following infection with HAV, HBV, HCV, HEV, HSV/HHV, CMV, EBV, and parvo-virus B19. The prevalence of HAV-induced ALF is markedly lower in countries with routine HAV immunization while HEV was the most common etiological cause of viral-induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which seem to increase with poor economic status of the studied countries.

The estimated prevalence of HAV-induced ALF in countries with routine HAV immunization was markedly lower than the estimated prevalence in countries without routine HAV immunization. When looking at countries with data before and after the introduction of routine HAV immunization, the reduction of HAV-induced ALF due to vaccination is further highlighted. The combined prevalence of HBV-induced ALF was the same in settings with or without universal HBV immunization. Countries without universal HBV immunization programs are likely to have weak healthcare systems; thus, the reported prevalence of HBV-induced ALF is assumed to be an underestimate of the true burden in these populations due to weak routine testing and reporting systems. Currently, there is one HEV vaccine (Hecolin) licensed in China that has shown promise with a high degree of efficacy in preventing HEV genotype IV infection in healthy individuals 16 to 65 years (15). Further exploration of the efficacy of this vaccine for prevention of infection with genotypes I and II in different populations should to explore it's application in different countries and HEV endemicity settings (16).

This review estimated the mortality rate for viral-induced ALF to be approximately 50% in low- and middle- income countries (LMICs) and less than 30% in upper-middle- and high-income countries. Previous studies have estimated that mortality rates associated with ALF vary between 60% and 80%, depending on the disease etiology as well as a patient's access to care. Our review shows that although viral-induced ALF still carries a significant mortality, though possibly lower than that reported for other ALF etiologies (5, 6). Mortality data largely comes from hospitals with the capacity to diagnose viral-

induced ALF, thus deaths outside of the hospital system or ALF deaths without virological testing may not be captured in these mortality estimates. Liver transplantation is required by approximately 25% of viral-induced ALF cases and approximately 18% of viral-induced ALF cases required renal transplantation, globally. In addition to general lack of resources for transplantation, a significant proportion of potential candidates have contraindications to transplant related to poor socioeconomic status in LMICs. The transplant data included in this review may only reflect successful and unsuccessful transplants, not those that were needed but not carried out due to resource constraints or contraindications.

This review is limited by lack of data for some of the viral etiologies of ALF including for VZV, HPIVs, YFV, CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced ALF. Additionally, we believe that our findings underestimate the global burden of viral-induced ALF as some important causes of ALF (e.g. HSV/HHV) are believed to be underrecognized as they require PCR testing for diagnosis. The included studies also used varying methods of virus detection including serology and molecular tests which further added to the heterogeneity in the results of our review. This is a well-recognized limitation in studies of ALF where diagnostics are often limited by cost in under-resourced regions where viral causes of ALF are more prevalent. The limited availability of data, including lack of same country data on burden of disease before and after introduction of immunization, hindered most of the planned sub-group analyses outlined in the study protocol. Where data were available, high heterogeneity of the data led to planned meta-analyses and meta-regression analyses not being possible. Lastly, the diversity of viruses attributable to ALF cases led to low statistical power in meta-analyses conducted.

Future research should assess the burden of viral-induced ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and HAdVs. Collectively, high-quality data on all viral etiologies of ALF would allow for better pooling of results. The review team encourages future studies to incorporate health economic estimates and mathematical modelling where data permits to assist health policy decision-makers to better design strategies for the prevention and management of viral-induced ALF. Epidemiological-economic modelling of immunization against HAV, HBV and HEV may well show that introduction of vaccination could lead to future cost savings in the long run due to prevented medical care and liver failure.

**Conclusions**

We successfully addressed the aim of the study although data on VZV, HPIVs, YFV, CA16 and/or HAdVs were missing. Notwithstanding the noted limitations, it is clear that HAV, HBV and HEV – vaccine-preventable ALF etiologies – account for a large proportion of ALF (approximately 21%, 20%, 32% of viral-induced ALF cases, respectively). The burden of ALF that is associated with vaccine-preventable ALF etiologies should be used in conjunction with other available key evidence to inform practice and policies on immunization, particularly in LMICs. A majority of LMICs have established universal vaccination against HBV. The Word Health Organization has recently recommended the introduction of an HBV birth dose which is aimed at elimination of the virus and, if successful, will subsequently reduce the burden of HBV-induced ALF. Routine HAV immunization in LMICs, however, are lacking. More data is urgently needed to guide routine use of the vaccine in prevention of morbidity and mortality caused by the virus. Lastly, further applicability of HEV vaccines should be explored, especially in LMICs where resources for managing viral-induced ALF are glaringly lacking.

**Contributors**

JP, GDH, BK and RM conceived this study. JP implemented the review under the supervision of RM. JP and HSH performed the study search, screening and extraction of data under the guidance of RM. GDH and BK provided methodological expertise for this review. SS, LG, MS, and WS provided content expertise for this review and all authors will provided comments on the final manuscript before publication. JP is the guarantor of this review.

**Funding**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The Vaccines for Africa Initiative (VACFA) has funded the costs associated with the research and dissemination of the results, including publications.

**Competing interests**

None declared.

**Data availability**

All data were taken from published articles available in the public domain.

**Patient consent for publication**

Not required.

## REFERENCES


1. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology. 2017;66(5):1047-81.
2. Morabito V, Adebayo D. Fulminant Hepatitis: Definitions, Causes and Management. Health. 2014;06(10):1038-48.
3. European Association for the Study of the Liver. Electronic address eee, Clinical practice guidelines p, Wendon J, Panel m, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047-81.
4. Cervio G, Trentadue J, D'Agostino D, Luque C, Giorgi M, Armoni J, et al. Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program. Hepat Med. 2011;3:99-106.
5. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet. 2010;376(Seminar):190-201.
6. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. Systematic review: acute liver failure - one disease, more than 40 definitions. Aliment Pharmacol Ther. 2012;35(11):1245-56.
7. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012;55(3):965-7.
8. Spearman CW, McCulloch M, Millar AJ, Burger H, Numanoglu A, Goddard E, et al. Liver transplantation at Red Cross War Memorial Children's Hospital. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2006;96(9 Pt 2):960-3.
9. O'Grady JG. Acute liver failure. Postgrad Med J. 2005;81(953):148-54.
10. O'Grady J. Liver transplantation for acute liver failure. Best Pract Res Clin Gastroenterol. 2012;26(1):27-33.
11. Patterson J, Hussey HS, Abdullahi LH, Silal S, Goddard L, Setshedi M, et al. The global epidemiology of viral-induced acute liver failure: a systematic review protocol. BMJ Open. 2019.
12. Balk E, Ching M, Chen M, Trikalinos T, L KWC. Assessing the Accuracy of Google Translate to Allow Data Extraction From Trials Published in Non-English Languages. Rockville, USA: Agency for Healthcare Research and Quality; 2013 Jan 2013. Contract No.: EHC145-EF.
13. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C. Assessing risk of bias in prevalence studies: Modification of an existing tool and evidence of interrater aggreement. Journal of Clinical Epidemiology. 2012;65:934-9.
14. Werfalli M, Musekiwa A, Engel ME, Ross I, Kengne AP, Levitt NS. The prevalence of type 2 diabetes mellitus among older people in Africa: a systematic review study protocol. BMJ Open. 2014.
15. Li SW, Zhao Q, Wu T, Chen S, Zhang J, Xia NS. The development of a recombinant hepatitis E vaccine HEV 239. Hum Vaccin Immunother. 2015;11(4):908-14.
16. Wu X, Chen P, Lin H, Hao X, Liang Z. Hepatitis E virus: Current epidemiology and vaccine. Human Vaccines and Immunotherapeutics. 2016;12(10):2603-10.
17. Alam S, Azam G, Mustafa G, Azad AK, Haque I, Gani S, et al. Natural course of fulminant hepatic failure: the scenario in Bangladesh and the differences from the west. Saudi J Gastroenterol. 2009;15(4):229-33.
18. Asim M, Singla R, Gupta RK, Kar P. Clinical & molecular characterization of human TT virus in different liver diseases. Indian Journal of Medical Research. 2010;131(4):545-54.
19. Bechmann LP, Manka P, Best J, Saner FH, Paul A, Canbay A, et al. Drug-induced liver injury as predominant cause of acute liver failure in a monocenter study. Deutsche Medizinische Wochenschrift. 2014;139(17):878-82.
20. Bhatia V, Dhawan A, Arora NK, Mathur P, Das MK, Irshad M. Urinary potassium loss in children with acute liver failure and acute viral hepatitis. J Pediatr Gastroenterol Nutr. 2013;57(1):102-8.
21. Borkakoti JH, R. K.; Mohammad, A.; Kumar, A.; Kar, P. Does high viral load of hepatitis E virus influence the severity and prognosis of acute liver failure during pregnancy? Journal of Medical Virology. 2013;85(4):620-6.
22. Bravo LC, Gregorio GV, Shafi F, Bock HL, Boudville I, Liu Y, et al. Etiology, incidence and outcomes of acute hepatic failure in 0-18 year old Filipino children. Southeast Asian J Trop Med Public Health. 2012;43(3):764-72.
23. Das AK, Begum T, Kar P, Dutta A. Profile of Acute Liver Failure from North-east India and Its Differences from other Parts of the Country. Euroasian J Hepatogastroenterol. 2016;6(2):111-5.
24. Gupta P, Mittal M, Bhat NK, Agarwal RK, Gupta P, Mittal G. A hospital based retrospective study on hepatotropic viruses as a cause of acute viral hepatitis in children in Uttarakhand, India. Indian Journal of Community Health. 2015;27(4):451-5.
25. Ho CM, Lee CH, Wang JY, Lee PH, Lai HS, Hu RH. Nationwide longitudinal analysis of acute liver failure in taiwan. Medicine (Baltimore). 2014;93(4):e35.
26. Latif N, Mehmood K. Risk factors for fulminant hepatic failure and their relation with outcome in children. J Pak Med Assoc. 2010;60(3):175-8.
27. Mamun Al M, Rahman S, Khan M, Karim F. HEV infection as an aetiologic factor for acute hepatitis: experience from a tertiary hospital in Bangladesh. J Health Popul Nutr. 2009;27(1):14-9.
28. Manka P, Bechmann LP, Coombes JD, Thodou V, Schlattjan M, Kahraman A, et al. Hepatitis E Virus Infection as a Possible Cause of Acute Liver Failure in Europe. Clin Gastroenterol Hepatol. 2015;13(10):1836-42.e2; quiz e157-8.
29. Mendizabal MM, S.; Videla, M. G.; Anders, M.; Zerega, A.; Balderramo, D. C.; Chan, D.; Barrabino, M.; Gil, O.; Mastai, R.; Yantorno, S.; Gadano, A.; Silva, M. O. Changing etiologies and outcomes of acute liver failure: Perspectives from 6 transplant centers in Argentina. Liver Transplantation. 2014;20(4):483-9.
30. Mishra SB, J.; Kumar, S.; Kar, P. Role of HEV antigen detection in HEV-related acute viral hepatitis and acute liver failure. Journal of Medical Virology. 2016;88(12):2179-85.
31. Mumtaz K, Azam Z, Hamid S, Abid S, Memon S, Ali Shah H, et al. Role of N-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. Hepatology International. 2009;3(4):563-70.
32. Pandit A, Mathew LG, Bavdekar A, Mehta S, Ramakrishnan G, Datta S, et al. Hepatotropic viruses as etiological agents of acute liver failure and related-outcomes among children in India: a retrospective hospital-based study. BMC Res Notes. 2015;8:381.

33. Poovorawan Y, Chongsrisawat V, Shafi F, Boudville I, Liu Y, Hutagalung Y, et al. Acute hepatic failure among hospitalized Thai children. Southeast Asian J Trop Med Public Health. 2013;44(1):50-3.
34. Schwarz KBO, Dominic Dell; Lobritto, Steven J.; Lopez, M. James; Rodriguez-Baez, Norberto; Yazigi, Nada A.; Belle, Steven H.; Zhang, Song; Squires, Robert H.; for the Pediatric Acute Liver Failure Study, Group. Analysis of Viral Testing in Nonacetaminophen Pediatric Acute Liver Failure. Journal of Pediatric Gastroenterology & Nutrition. 2014;59(5):616-23.
35. Shalimar, Kedia S, Gunjan D, Sonika U, Mahapatra SJ, Nayak B, et al. Acute Liver Failure Due to Hepatitis E Virus Infection Is Associated with Better Survival than Other Etiologies in Indian Patients. Dig Dis Sci. 2017;62(4):1058-66.
36. Silverio CE, Smithen-Romany CY, Hondal NI, Diaz HO, Castellanos MI, Sosa O. Acute liver failure in Cuban children. MEDICC Rev. 2015;17(1):48-54.
37. Somasekar SL, D.; Rule, J.; Naccache, S. N.; Stone, M.; Busch, M. P.; S.; ers, C.; Lee, W. M.; Chiu, C. Y. Viral Surveillance in Serum Samples from Patients with Acute Liver Failure by Metagenomic Next-Generation Sequencing. Clinical Infectious Diseases. 2017;65(9):1477-85.
38. Uddin Jamro BMC, S.; Mal Makheja, P.; Ahmed Soomro, A. Etiology, outcome and risk factors for fulminant hepatic failure in children at a tertiary care hospital, Sukkur, Pakistan. Rawal Medical Journal. 2013;38(3):219-22.
39. Tsunoda T, Inui A, Iwasawa K, Oikawa M, Sogo T, Komatsu H, et al. Acute liver dysfunction not resulting from hepatitis virus in immunocompetent children. Pediatr Int. 2017;59(5):551-6.
40. Zhao P, Wang CY, Liu WW, Wang X, Yu LM, Sun YR. Acute liver failure in Chinese children: a multicenter investigation. Hepatobiliary Pancreat Dis Int. 2014;13(3):276-80.

**FIGURE LEDENDS**

Figure 1: Flow diagram for selection of studies

Figure 2: Prevalence of HAV-induced ALF by country HAV immunization status

- Abbreviations: HAV = hepatitis A virus, ALF = acute liver failure, CI = confidence interval, I2 = heterogeneity statistic

Figure 3: Prevalence of HBV-induced ALF by country HBV immunization status

- Abbreviations: HBV = hepatitis B virus, ALF = acute liver failure, CI = confidence interval, I2 = heterogeneity statistic

Figure 4: Prevalence of outcomes associated with viral-induced ALF

- Abbreviations: ALF = acute liver failure, CI = confidence interval, I2=heterogeneity statistic, NA = not applicable

## TABLES

**Table 1: Characteristics of included studies**

| Study | Study Design | Aim | Country | Income Level | Start of Data Collection | End of Data Collection | ALF Case Definition |
|---|---|---|---|---|---|---|---|
| Alam et al., 2009 (17) | Prospective cohort | To evaluate the etiology, complications, and outcome of FHF | Bangladesh | Lower-middle | 3-Nov | 8-May | Occurrence of hepatic encephalopathy within 8 weeks of onset of jaundice in patients with no previous liver disease and the presence of coagulopathy as proved by a PT > 15 s or INR > 1.5 |
| Asim et al., 2009 (18) | Cross-sectional | To analyze serum samples from patients with ALF for hepatitis A-G viral markers | India | Lower-middle | 1-Jun | 4-May | Patient become deeply jaundiced and went into hepatic encephalopathy within 8 weeks of onset of the disease, with no past history of chronic hepatitis |
| Bechmann et al., 2014 (19) | Retrospective cohort | To identify currently predominant etiologies of ALF at a transplant center | Germany | High | 1-Jan | 12-Feb | *Acute Liver Failure Study Group Germany* case definition: INR > 1.5 and encephalopathy of any grade. Pre-existing liver disease and systemic cause of liver failure were excluded |
| Bhatia et al., 2013 (20) | Prospective cohort | To analyze clinical features, liver function tests, hepatitis viral markers and clinical outcomes in patients with ALF | India | Lower-middle | Jun-99 | 1-Jan | Development of hepatic encephalopathy within 26 weeks of the first symptoms of acute hepatitis-like illness without any history of underlying liver disease |
| Borkakoti et al., 2013 (21) | Prospective cohort | To determine the viral load of HEV and its association with the disease severity in patients with ALF in comparison with patients with ALF due to other hepatides | India | Lower-middle | 6-Jan | 11-Dec | Development of encephalopathy within 8 weeks of the onset of jaundice without any past history of chronic liver disease; diagnosed as a self-limiting disease and a serum aspartate aminotransferase elevation of at least fivefold or clinical jaundice or both |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Bravo et al., 2012 (22) | Prospective & retrospective cohort | To investigate the etiology, outcomes and incidence of AHF among children 0-18 years old | Philippines | Lower-middle | Jan-00 | 6-Dec | Onset of coagulopathy and/or encephalopathy ≤4 weeks after the onset of symptoms, a prothrombin time > 2, an increased bilirubin and evidence for liver failure complicated by encephalopathy |
| Cervio et al., 2011 (4) | Retrospective cohort | To investigate the impact of HAV UI on the trends in the occurrence of FHF in children | Argentina | High | Mar-93 | 5-Jul | *Mieli-Vergani* case definition: a multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in a patient with or without recognized underlying chronic liver disease (**Cheeseman & Mieli-Vergani, 2004**) |
| Das et al., 2016 (23) | Prospective cohort | To determine the profile of ALF etiologies | India | Lower-middle | 7-Jan | 15-Dec | History of development of encephalopathy within 8 weeks of disease onset |
| Gupta et al., 2015 (24) | Retrospective cohort | To determine the profile of Hepatitis A, B, C and E as a cause of AHF in children in a tertiary care hospital | India | Lower-middle | 11-Jan | 14-Dec | Elevated ALT levels or AST of at least five-fold with clinical jaundice and without evidence of chronic liver disease. Patients who had INR > 1.5 with encephalopathy or INR > 2 without encephalopathy |
| Ho et al., 2014 (25) | Prospective cohort | To investigate the incidence, etiology, outcomes, and prognostic factors of ALF | Taiwan | High income | 5-Jan | 7-Sep | International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 570.0 |
| Latif et al., 2010 (26) | Prospective cohort | To identify the risk factors for FHF and their relationship with the outcome in children | Pakistan | Lower-middle | 6-Sep | 7-Feb | Development of encephalopathy within 8 weeks of the onset of jaundice having evidence of coagulopathy i.e. PT deranges > 4 s of control and deranged liver function i.e. TSB > 1.5 mg/dl, AT > 40 IU/L |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mamun et al., 2009 (27) | Retrospective cohort | To assess the burden of HEV as a cause of ALF | Bangladesh | Lower-middle | 4-Jun | 6-Dec | Previously healthy patients who presented with severe impairment of hepato-cellular function, i.e. encephalopathy, coagulopathy, and jaundice, within six months of onset of symptoms |
| Manka et al., 2015 (28) | Retrospective cohort | To investigate the causes of previously diagnosed indeterminate cases ALF | Germany | High | 6-Nov | 13-Dec | Significant liver dysfunction with pathologically increased laboratory parameters [AST, ALT, AP], an existing coagulopathy in terms of an INR > 1.5, and with the concomitant presence of any degree of encephalopathy |
| Mendizabal et al., 2014 (29) | Retrospective cohort | To determine the causes and short-term outcomes of ALF | Argentina | High | 5-Jun | 11-Dec | Presence of coagulopathy [INR > 1.5 or prothrombin index < 50%] and any grade of HE within 26 weeks of the first symptoms without a known underlying liver disease |
| Mishra et al., 2016 (30) | Retrospective cohort | To assess the relative efficacy of HEV antigen detection by ELISA in patients with ALF | India | Lower-middle | 13-Nov | 15-Jan | Any evidence of coagulation abnormality, generally INR >1.5 and any degree of mental alteration (encephalopathy) without pre-existing cirrhosis and with an illness of < 4 weeks duration |
| Mumtaz et al., 2009 (31) | Prospective cohort compared to historical control | To assess the etiology, prothrombin time (PT), alanine aminotransferase, creatinine, albumin for non-acetaminophen-induced ALF | Pakistan | Lower middle | Jan-00 | 7-Mar | Rapid development of acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver |
| Pandit et al., 2015 (32) | Retrospective cohort | To assess the frequency of hepatotropic viruses as etiological agents of ALF | India | Lower-middle | 3-Jan | 5-Dec | Onset of encephalopathy ≤28 days after the onset of symptoms with INR > 2 and increased bilirubin complicated by encephalopathy in patients |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | without a previous history of liver disease |
| Poovorawan (33) et al., 2013 | Prospective cohort | To determine the causes and outcomes of Thai children with AHF | Thailand | Upper-middle | 2-Jan | 5-Sep | *International Association for the Study of the Liver* case definition: **(Tandon et al, 1999)** |
| Schwarz et al., 2014 (34) | Retrospective cohort - Patient registry | To analyzed results of viral testing among non-acetaminophen ALF study participants | USA/Canada/UK | High | Dec-99 | 12-Dec | No known evidence of chronic liver disease, with evidence of acute liver injury, and hepatic-based coagulopathy not corrected by vitamin K with the follow parameters: PT ≥ 15 s or INR ≥ 1.5 in the presence of clinical HE or a PT ≥ 20 s or INR ≥ 2.0 regardless of the presence or absence of clinical HE |
| Shalimar et al., 2017 (35) | Retrospective cohort | To assess the differences in the course of HEV-ALF as compared to other etiologies of ALF | India | Lower middle | Jan-86 | 15-Dec | *International Association for the Study of Liver* (IASL) case definition: Occurrence of encephalopathy within 4 weeks from the onset of symptoms in the absence of preexisting liver disease |
| Silverio et al., 2015 (36) | Retrospective cohort | To describe the clinical features of children treated for ALF | Cuba | Upper-middle | 5-Jan | 11-Dec | Evidence of liver damage in the absence of prior known chronic liver disease; altered coagulation, expressed as PT >15 s with encephalopathy; or PT > 20 s with or without encephalopathy—all this within eight weeks of onset of clinical symptoms |
| Somasekar et al., 2017 (37) | Retrospective cohort | To investigate the causes of previously diagnosed indeterminate cases ALF | United States | High | Jan-98 | 10-Dec | *United States Acute Liver Failure Study Group* case definition |
| Uddin Jamro et al., 2013 (38) | Retrospective cohort | To study the etiology, outcome and risk factors for FHF in children at | Pakistan | Lower-middle | 7-Jul | 12-Jun | Presence of acute liver failure (coagulopathy PT > 20 s or INR > 2), HE without pre-existing liver disease, within 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | a tertiary care hospital | | | | | weeks of the onset of clinical liver disease |
| Tsunoda et al., 2017 (39) | Prospective cohort | To identify the roles of CMV, EBV and HHV in immunocompetent children with acute liver failure not resulting from hepatitis virus | Japan | High | 7-Jan | 13-Dec | Liver dysfunction with elevated AST and ALT > 30 IU/L |
| Zhao et al., 2014 (40) | Retrospective cohort | To investigate etiologies and outcomes of children with ALF | China | Middle | 7-Jan | 12-Dec | Coagulopathy [PTA ≤40% or INR ≥ 1.5 excluding hematologic diseases] and jaundice [Tbil ≥ 171 μmol/L] within 4 weeks in a child without pre-existing liver diseases |

**Abbreviations:** ALF = acute liver failure; FHF = fulminant hepatic failure; AHF = acute hepatic failure; HEV = hepatitis E virus; CMV = cytomegalovirus; EBV = Epstein Barr virus; HHV = human herpesvirus; ELISA = enzyme-linked immunosorbent assay; INR = international normalized ratio; PT = prothrombin time; s = second; TSB = total serum bilirubin; HE = hepatic encephalopathy; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP = alkaline phosphatase; PTA = plasma thromboplastin antecedent

Figure 1: Flow diagram for selection of studies

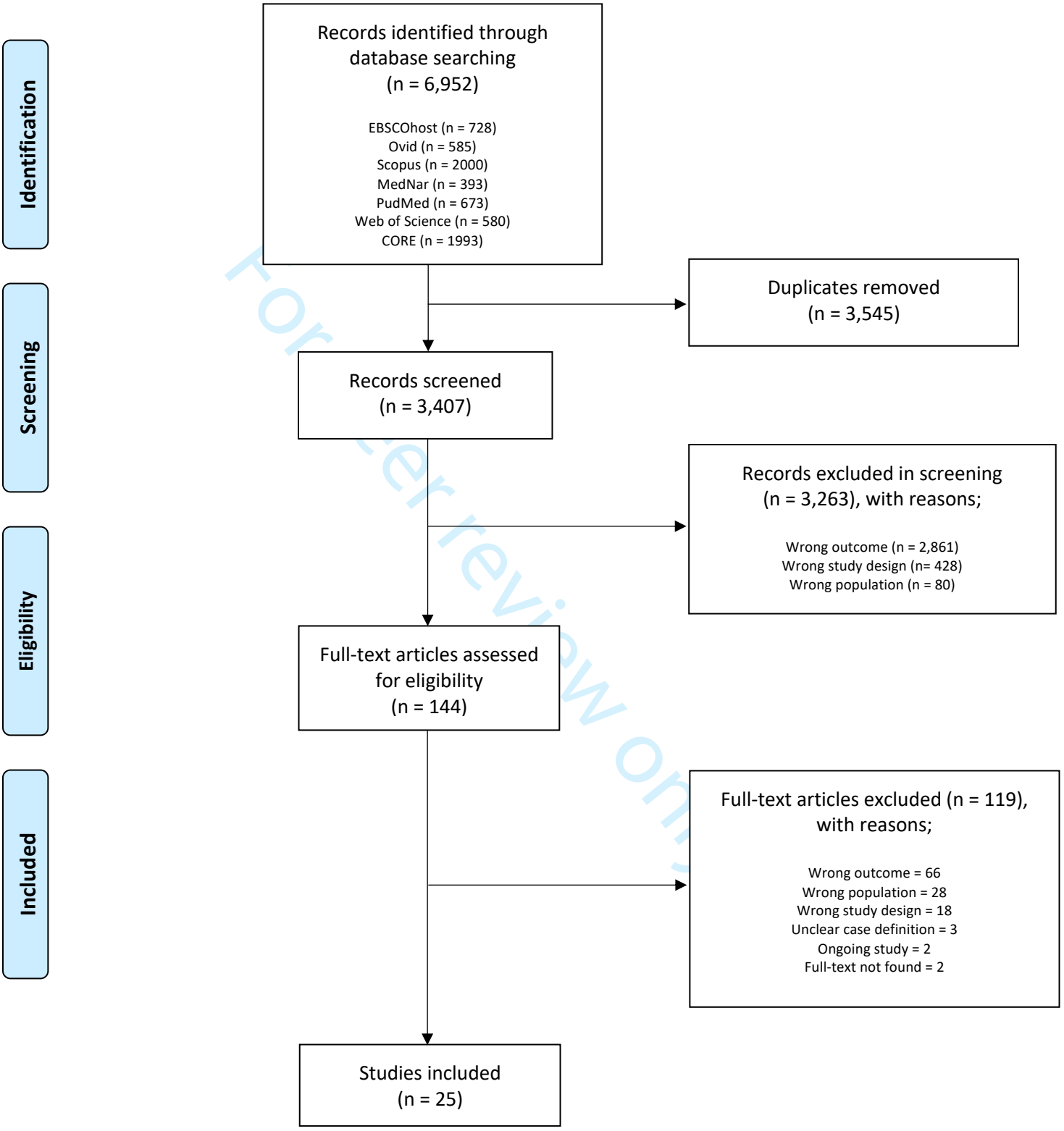


Figure 2: Prevalence of HAV-induced ALF by country HAV immunization status

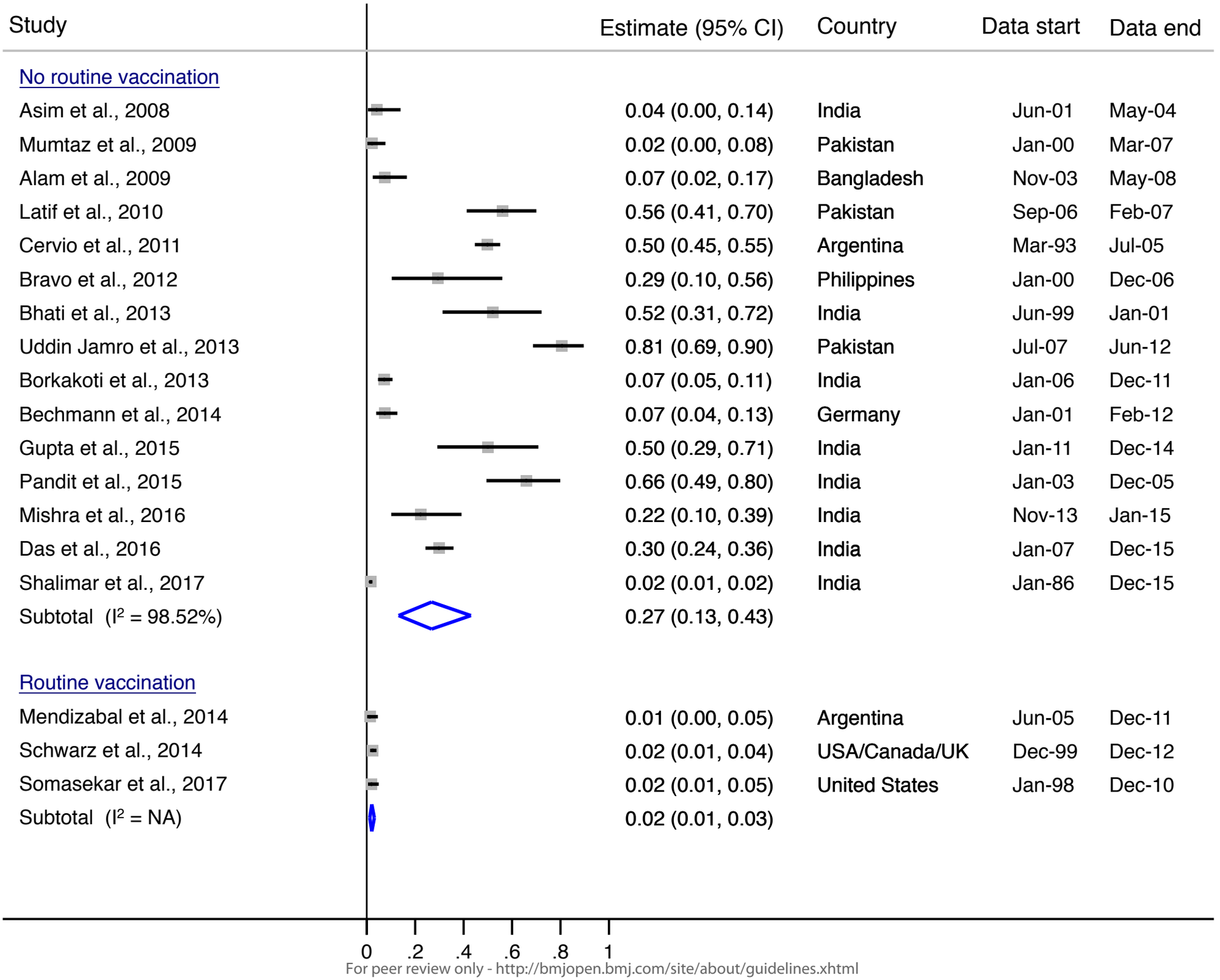
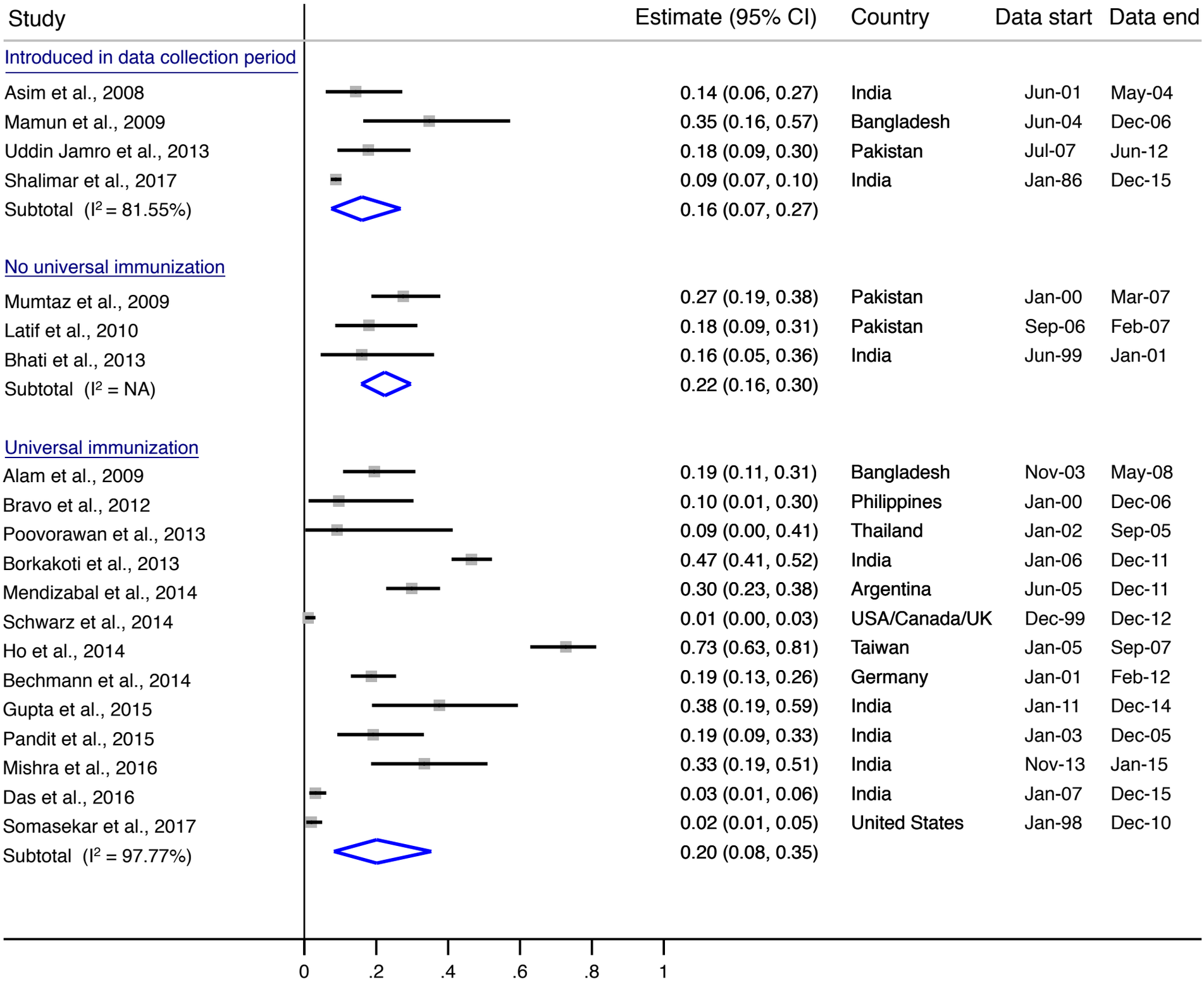
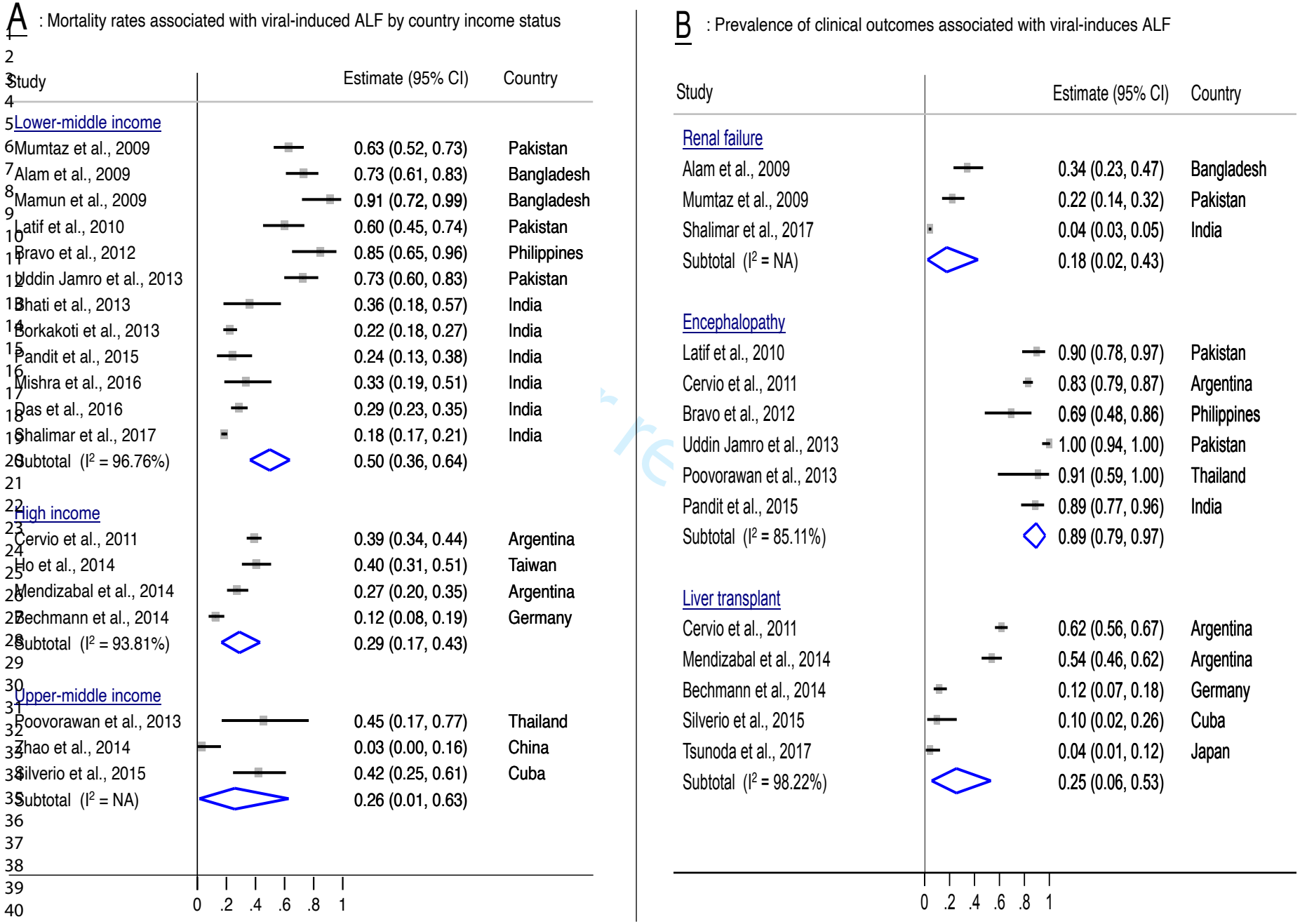


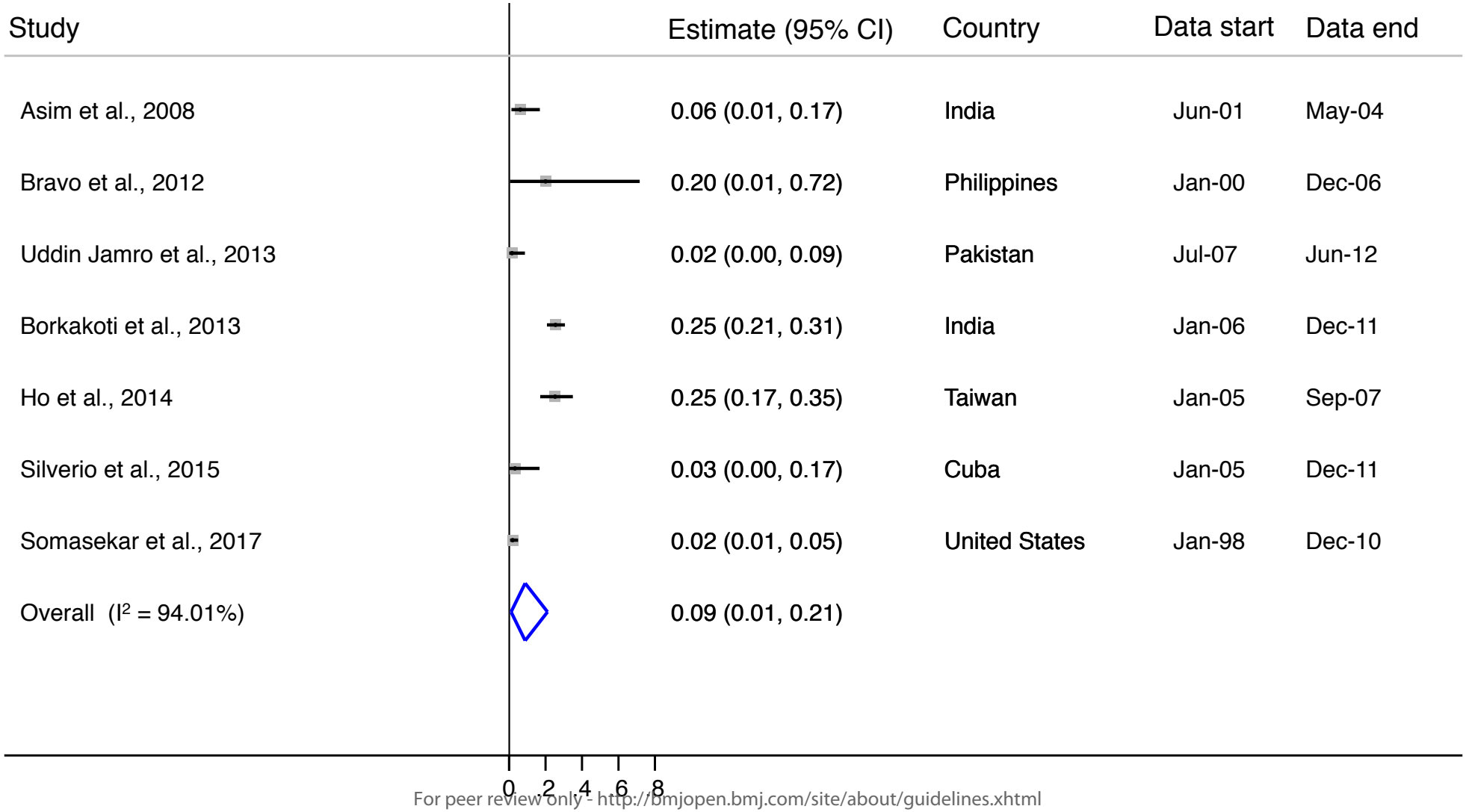
Figure 3: Prevalence of HBV-induced ALF by country HBV immunization status



# Figure 4: Prevalence of outcomes associated with viral-induced ALF



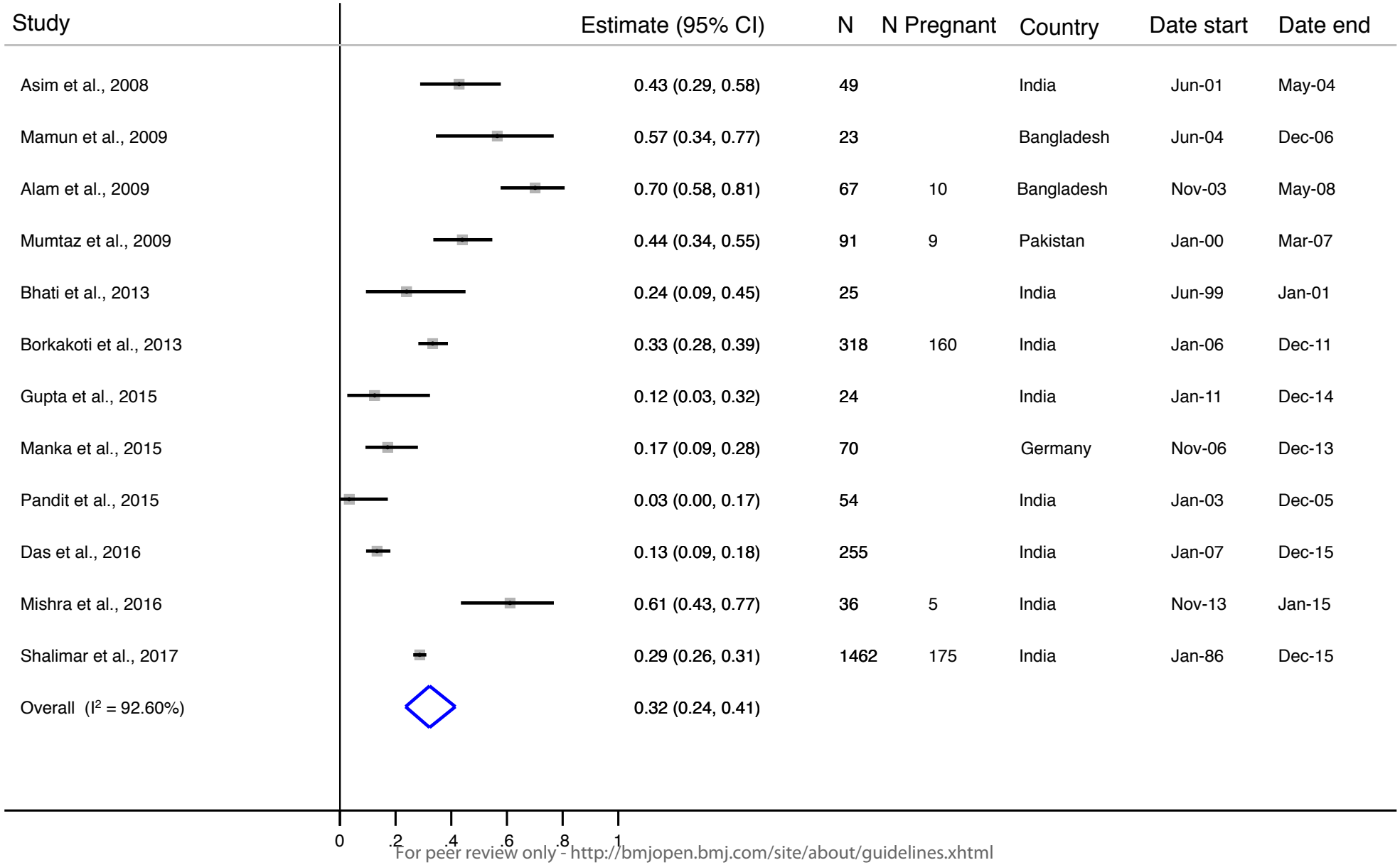
# Supplementary Figure 1: Prevalence of HCV-induced ALF






Abbreviations: HCV = hepatitis C virus, ALF = acute liver failure, CI = confidence interval, $I^2$ = heterogeneity statistic

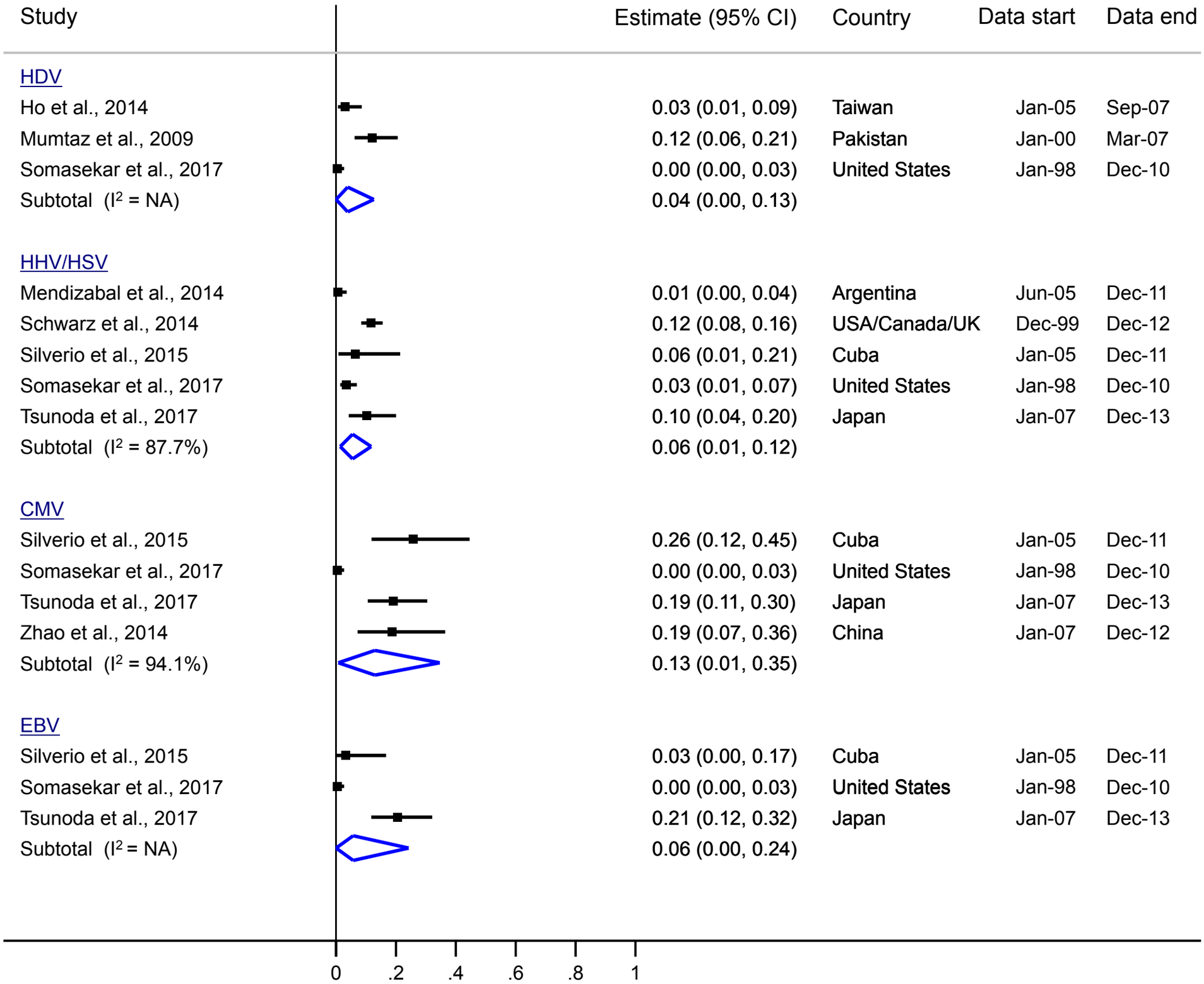
# Supplementary Figure 2: Prevalence of HEV-induced ALF






Abbreviations: HEV = hepatitis E virus, ALF = acute liver failure, CI = confidence interval, $I^2$ = heterogeneity statistic

# Supplementary Figure 3: Prevalence of HDV-, HHV/HSV-, CMV- and EBV-induced AFL






Abbreviations: HDV = hepatitis D virus, HHV/HSV = Human Herpes virus/Herpes Simplex Virus, CMV = Cytomegalovirus, EBV = Epstein-Barr virus,

## SUPPLEMENTARY TABLE

**Supplementary Table 1: Risk of bias judgements for included studies**

| Study ID | Representation of the national population | Representation of target population | Random selection or census | Minimal likelihood of non-response bias | Data collected directly from participants | Acceptable case definition | Valid measurement | Same mode of data collection | Appropriate length | Appropriate numerator(s) and denominator(s) | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alam et al., 2009 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Asim et al., 2009 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Bechmann et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Bhati et al., 2013 | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Borkakoti et al., 2013 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Bravo et al., 2012 | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Cervio et al., 2011 | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Das et al., 2016 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Gupta et al., 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Ho et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Latif et al., 2010 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Mamun et al., 2009 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Manka et al., 2015 | No | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | 8 |
| Mendizabal et al., 2014 | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Mishra et al., 2016 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 7 |
| Mumtaz et al., 2009 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Pandit et al., 2015 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Poovorawan et al., 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 9 |
| Schwarz et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 9 |
| Shalimar et al., 2017 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Silverio et al., 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Somasekar et al., 2017 | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Uddin Jamro et al., 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Tsunoda et al., 2017 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Zhao et al., 2014 | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |

**The PRISMA for Abstracts Checklist**

| TITLE | CHECKLIST ITEM | REPORTED ON PAGE # |
|---|---|---|
| 1. Title: | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **BACKGROUND** | | |
| 2. Objectives: | The research question including components such as participants, interventions, comparators, and outcomes. | 1 |
| **METHODS** | | |
| 3. Eligibility criteria: | Study and report characteristics used as criteria for inclusion. | 1 |
| 4. Information sources: | Key databases searched and search dates. | 1 |
| 5. Risk of bias: | Methods of assessing risk of bias. | 1 |
| **RESULTS** | | |
| 6. Included studies: | Number and type of included studies and participants and relevant characteristics of studies. | 1 |
| 7. Synthesis of results: | Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals. | 1 |
| 8. Description of the effect: | Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients. | 1 |
| **DISCUSSION** | | |
| 9. Strengths and Limitations of evidence: | Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence) | 1 |
| 10. Interpretation: | General interpretation of the results and important implications | 1 |
| **OTHER** | | |
| 11. Funding: | Primary source of funding for the review. | 1 |
| 12. Registration: | Registration number and registry name. | 1 |

# PRISMA 2009 Checklist

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

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 4 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 4-5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 4 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 5 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 6 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 5-6 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 5-6 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 5-6 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 6-8 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 8 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 10 |

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

# PRISMA 2009 Checklist

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