

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
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 Hussey, Hannah; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health & Family Medicine Silal, Sheetal; University of Cape Town, Department of Statistical Sciences; University of Oxford, Nuffield Department of Medicine Goddard, Liz; University of Cape Town, Department of Paediatrics, Red Cross War Memorial Children's Hospital Setshedi, Mashiko; University of Cape Town, Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital Spearman, Wendy ; University of Cape Town, Department of Medicine, Division of Hepatology, Groote Schuur Hospital Hussey, Gregory; University of Cape Town 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 Kagina, Benjamin; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine Muloiswa, 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 Initiative, School of Public Health and Family Medicine
Keywords:	Epidemiology < INFECTIOUS DISEASES, Hepatology < INTERNAL MEDICINE, VIROLOGY

SCHOLARONE™
Manuscripts



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 Goddard⁵, Mashiko Setshedi⁶, C. Wendy Spearman⁷, Gregory D. Hussey^{1,8} Benjamin M. Kagina^{1,2} and Rudzani Muloiwa^{1,5}

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

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

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

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

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

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

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

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

⁵Department 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.

1
2
3 50 *Bernal et al. 2010* completed a review of the burden of acute and fulminant liver failure based on
4
5 51 literature published between 1997 and 2009. The review became the bases for guidelines for clinical
6
7 52 practice (5). In this systematic review, we assess whether data have changed following the Bernal
8
9 53 publication, and whether there is evidence to warrant a review of clinical practice.

10 11 54 **Objectives**

- 12 55 • To estimate the prevalence of hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus
13 56 (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex
14 57 virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19,
15 58 human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6),
16 59 cytomegalovirus (CMV), coxsackievirus (CA16) and/or adenovirus (HAdVs) among patients with
17 60 ALF.
- 18 61 • To estimate the mortality rate for cases of ALF following infection with HAV, HBV, HCV, HDV,
19 62 HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs
- 20 63 • To estimate the prevalence and incidence of liver transplantation for cases of ALF following
21 64 infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV,
22 65 HHV-6, CMV, CA16 and/or HAdVs

23 66 24 67 **Methods**

25 68 This systematic review was registered with PROSPERO (registration number CRD42017079730) and the
26 69 methods for its conduction have been published (11). The results of the review are reported using the
27 70 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines checklist
28 71 (**Appendix 1**).

29 72 30 73 **Study eligibility criteria**

31 74 Published cross-sectional, surveillance and cohort studies reporting the outcomes of interest in patients
32 75 with ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19,
33 76 HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs were eligible for inclusion in this study. Studies were
34 77 eligible for inclusion if they had clearly stated case definitions of viral-induced ALF and confirmed ALF
35 78 cases using both clinical and serological, molecular or culture diagnostic methods.

36 79 37 80 **Search strategy**

1
2
3 81 A combination of the following search terms (including the use of Medical Subject Headings (MESH))
4
5 82 was used and adapted for each of the relevant electronic databases: epidemiology, prevalence,
6
7 83 incidence, burden, mortality, morbidity, fulminant hepatic failure, fulminant liver failure, acute hepatic
8
9 84 failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV),
10
11 85 hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex virus-1 (HSV1),
12
13 86 herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses
14
15 87 (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), coxsackie virus
16
17 88 and adenovirus.

18
19 90 The following electronic databases were searched for relevant literature published from 2009 to 2019:
20
21 91 EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The search was run on 9 April 2019 and
22
23 92 updated via PubMed on 30 September 2019 with no new eligible studies to include.

24 93

25 94 **Data extraction**

26
27 95 Study characteristics and outcomes of interests were extracted from the included studies on a pre-
28
29 96 designed data extraction form by two independent reviewers (JP and HH). Prior to use by the two
30
31 97 reviewers, the reliability of the extraction form was assessed by piloting 10 randomly selected articles
32
33 98 that met the inclusion criteria. The study team resolved any disagreements in data extraction through
34
35 99 consensus in consultation with RM. In cases where studies were in German, HH provided translation. In
36
37 100 cases where studies were not available in English or German, google translate was used to translate the
38
39 101 article to English (12).

40 102

41 103 **Data synthesis and analysis**

42 104 A random-effects model was fitted to the study data as it included data taken from a series of
43
44 105 independently performed studies in different populations. We assessed heterogeneity by calculating I^2
45
46 106 statistics (threshold $I^2 > 40\%$). The values of I^2 were categorized for heterogeneity as follows: “not
47
48 107 important” (0 to 40%), “moderate” (41 to 60%) and “considerable” (61 to 80%) and “substantial” (81 to
49
50 108 100%). Where “not important” or “moderate” heterogeneity existed between studies ($I^2 \leq 40\%$), pooled
51
52 109 outcome measures were reported with 95% confidence intervals for each respective outcome. Where
53
54 110 “considerable” or “substantial” heterogeneity exists between studies ($I^2 > 40\%$), forest plots and
55
56 111 prevalence ranges calculated using the random-effects model were used to narratively describe each
57
58 112 outcome.

113 **Risk of bias assessment**

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

119

120 **Results**

121 **Patient and public involvement**

122 This review was developed as part of an ongoing project by the research team that aims to generate
123 evidence to facilitate evidence-based decision-making of introducing routine hepatitis A vaccination in
124 South Africa. The findings of this review contribute to the knowledge base that aims to enhance global
125 vaccination strategies against viral-associated ALF. As this is a systematic review, no patient involvement
126 was required; however, it is hoped that the findings of this review will help to highlight the burden that
127 ALF places on populations without routine vaccination.

128

129 **Included studies**

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

140

141 **Vaccine-preventable viral-induced ALF**

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

1
2
3 145 countries with routine HAV immunization at the time of data collection ranged from 1% to 2% with an
4 average of 2% (95% CI 1, 3) (**Figure 2**). In Argentina, the prevalence of HAV-induced ALF prior to routine
5 146 immunization was approximately 50% (95% CI 45, 55), compared to approximately 1% (95% CI 0, 5) after
6 147 immunization was introduced. The point prevalence of HBV-induced ALF in countries without universal
7 148 HBV immunization at the time of data collection ranged from 16% to 27% with an average of 22% (95%
8 149 CI 16, 30) (**Figure 3**). The point prevalence of HBV-induced ALF in countries with universal HBV
9 150 immunization at the time of data collection ranged from 0% to 83% with an average of 19% (95% CI = 7,
10 151 36).
11 152
12 153

18 154 **ALF attributable to non-vaccine-preventable viral infections**

19 155 The point prevalence of HCV-induced ALF ranged from 2% to 25% with an average of 9% (95% CI = 1, 21)
20 156 (**Supplementary Figure 1**). The point prevalence of HEV-induced ALF ranged from 3% to 70% with an
21 157 average of 32% (95% CI 24, 41) (**Supplementary Figure 2**). The point prevalence of HDV-, HHV/HSV-,
22 158 CMV-, and EBV-induced ALF were estimated to have averages of 4% (95% CI 0, 13), 6% (95% CI 1, 12),
23 159 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),
24 160 respectively (**Supplementary Figure 3**). Data was not available to estimate the burden of ALF following
25 161 infection with HDV, VZV, HPIVS, YFV, CA16 and/or HAdVs as outlined per the published protocol (11).
26 162

33 163 **Outcomes of viral-induced ALF**

34 164 The narratively reported outcomes of viral-induced ALF were found to be severe. The mortality rates
35 165 associated with viral-induced ALF in lower-middle income countries ranged from 18% to 91% with an
36 166 average of 50% (95% CI 36, 64) (**Figure 4A**). The mortality rates associated with viral-induced ALF in
37 167 upper-middle income countries ranged 3% to 45% with an average of 26% (95% CI 1, 63) (**Figure 4A**).
38 168 The mortality rates associated with viral-induced ALF in high income countries ranged from 12% to 40%
39 169 with an average of 29% (95% CI 17, 43) (**Figure 4A**). The rate of encephalopathy associated with viral-
40 170 induced ALF cases in children ranged from 69% to 100% with an average of 89% (95% CI 79, 97) (**Figure**
41 171 **4B**). The need for liver transplantation with viral-associated ALF ranged from 4% to 62% with an average
42 172 of 25% (95% CI 6, 53) (**Figure 4B**). The need for renal transplant in viral-associated ALF cases ranged
43 173 from 4% to 34% with an average of 18% (95% CI 2, 43) (**Figure 4B**).
44 174

53 175 **Methodological quality**

1
2
3 176 Risk of bias scores were assigned by two reviewers (JP and HH) and are described in **Supplementary**
4
5 177 **Table 1**. Overall, a majority of the included studies were judged as having ‘low risk’ of bias. Only one
6
7 178 included study was judged as having ‘moderate risk’ of bias due to lack of clarity around the
8
9 179 representativeness of the study population to the national population, methods of participant selection
10
11 180 and methods employed to reduce the likelihood of non-response.
12

13 181

14 182 **Discussion**

15 183 This systematic review estimated the burden of ALF following infection with HAV, HBV, HCV, HEV,
16
17 184 HSV/HHV, CMV, EBV, and parvo-virus B19. The prevalence of HAV-induced ALF is markedly lower in
18
19 185 countries with routine HAV immunization while HEV was the most common etiological cause of viral-
20
21 186 induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by
22
23 187 high fatality rates, which seem to increase with poor economic status of the studied countries.
24

25 188

26 189 The estimated prevalence of HAV-induced ALF in countries with routine HAV immunization was
27
28 190 markedly lower than the estimated prevalence in countries without routine HAV immunization. When
29
30 191 looking at countries with data before and after the introduction of routine HAV immunization, the
31
32 192 reduction of HAV-induced ALF due to vaccination is further highlighted. The average prevalence of HBV-
33
34 193 induced ALF was the same in settings with or without universal HBV immunization. Countries without
35
36 194 universal HBV immunization programs are likely to have weak healthcare systems; thus, the reported
37
38 195 prevalence of HBV-induced ALF is assumed to be an underestimate of the true burden in these
39
40 196 populations due to weak routine testing and reporting systems. Currently, there is one HEV vaccine
41
42 197 (Hecolin) licensed in China that has shown promise with a high degree of efficacy in preventing HEV
43
44 198 genotype IV infection in healthy individuals 16 to 65 years (15). Further exploration of the efficacy of this
45
46 199 vaccine for prevention of infection with genotypes I and II in different populations should to explore it’s
47
48 200 application in different countries and HEV endemicity settings (16).

49 201

50 202 This review estimated the mortality rate for viral-induced ALF to be approximately 50% in low- and
51
52 203 middle- income countries (LMICs) and less than 30% in upper-middle- and high-income countries.
53
54 204 Previous studies have estimated that mortality rates associated with ALF vary between 60% and 80%,
55
56 205 depending on the disease etiology as well as a patient’s access to care. Our review shows that although
57
58 206 viral-induced ALF still carries a significant mortality, though possibly lower than that reported for other
59
60 207 ALF etiologies (5, 6). Mortality data largely comes from hospitals with the capacity to diagnose viral-

7

1
2
3 208 induced ALF, thus deaths outside of the hospital system or ALF deaths without virological testing may
4
5 209 not be captured in these mortality estimates. Liver transplantation is required by approximately 25% of
6
7 210 viral-induced ALF cases and approximately 18% of viral-induced ALF cases required renal
8
9 211 transplantation, globally. In addition to general lack of resources for transplantation, a significant
10
11 212 proportion of potential candidates have contraindications to transplant related to poor socioeconomic
12
13 213 status in LMICs. The transplant data included in this review may only reflect successful and unsuccessful
14
15 214 transplants, not those that were needed but not carried out due to resource constraints or
16
17 215 contraindications.
18

19
20 216
21 217 This review is limited by lack of data for some of the viral etiologies of ALF including for VZV, HPIVs, YFV,
22
23 218 CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced
24
25 219 ALF. Additionally, we believe that our findings underestimate the global burden of viral-induced ALF as
26
27 220 some important causes of ALF (e.g. HSV/HHV) are believed to be underrecognized as they require PCR
28
29 221 testing for diagnosis. The included studies also used varying methods of virus detection including
30
31 222 serology and molecular tests which further added to the heterogeneity in the results of our review. This
32
33 223 is a well-recognized limitation in studies of ALF where diagnostics are often limited by cost in under-
34
35 224 resourced regions where viral causes of ALF are more prevalent. The limited availability of data hindered
36
37 225 most of the planned sub-group analyses outlined in the study protocol. Where data were available, high
38
39 226 heterogeneity of the data led to planned meta-analyses and meta-regression analyses not being
40
41 227 possible. Lastly, the diversity of viruses attributable to ALF cases led to low statistical power in meta-
42
43 228 analyses conducted.
44

45 229
46 230 Future research should assess the burden of viral-induced ALF following infection with HDV, VZV, HPIVs,
47
48 231 YFV, CA16 and HAdVs. Collectively, high-quality data on all viral etiologies of ALF would allow for better
49
50 232 pooling of results. The review team encourages future studies to incorporate health economic estimates
51
52 233 and mathematical modelling where data permits to assist health policy decision-makers to better design
53
54 234 strategies for the prevention and management of viral-induced ALF. Epidemiological-economic
55
56 235 modelling of immunization against HAV, HBV and HEV may well show that introduction of vaccination
57
58 236 could lead to future cost savings in the long run due to prevented medical care and liver failure.
59

60 237

61 238 **Conclusions**

1
2
3 239 We successfully addressed the aim of the study although data on VZV, HPIVs, YFV, CA16 and/or HAdVs
4
5 240 were missing. Notwithstanding the noted limitations, it is clear that HAV, HBV and HEV – vaccine-
6
7 241 preventable ALF etiologies – account for a large proportion of ALF (approximately 21%, 20%, 32% of
8
9 242 viral-induced ALF cases, respectively). The burden of ALF that is associated with vaccine-preventable ALF
10
11 243 etiologies should be used in conjunction with other available key evidence to inform practice and
12
13 244 policies on immunization, particularly in LMICs. A majority of LMICs have established universal
14
15 245 vaccination against HBV. The World Health Organization has recently recommended the introduction of
16
17 246 an HBV birth dose which is aimed at elimination of the virus and, if successful, will subsequently reduce
18
19 247 the burden of HBV-induced ALF. Routine HAV immunization in LMICs, however, are lacking. More data is
20
21 248 urgently needed to guide routine use of the vaccine in prevention of morbidity and mortality caused by
22
23 249 the virus. Lastly, further applicability of HEV vaccines should be explored, especially in LMICs where
24
25 250 resources for managing viral-induced ALF are glaringly lacking.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 agreement. *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.

- 1
- 2
- 3
- 4 28. Mumtaz K, Azam Z, Hamid S, Abid S, Memon S, Ali Shah H, et al. Role of N-acetylcysteine in adults with non-
- 5 acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. *Hepatology*
- 6 *International*. 2009;3(4):563-70.
- 7 29. Pandit A, Mathew LG, Bavdekar A, Mehta S, Ramakrishnan G, Datta S, et al. Hepatotropic viruses as etiological agents
- 8 of acute liver failure and related-outcomes among children in India: a retrospective hospital-based study. *BMC Res*
- 9 *Notes*. 2015;8:381.
- 10 30. Poovorawan Y, Chongsrisawat V, Shafi F, Boudville I, Liu Y, Hutagalung Y, et al. Acute hepatic failure among
- 11 hospitalized Thai children. *Southeast Asian J Trop Med Public Health*. 2013;44(1):50-3.
- 12 31. Schwarz KBO, Dominic Dell; Lobritto, Steven J.; Lopez, M. James; Rodriguez-Baez, Norberto; Yazigi, Nada A.; Belle,
- 13 Steven H.; Zhang, Song; Squires, Robert H.; for the Pediatric Acute Liver Failure Study, Group. Analysis of Viral Testing
- 14 in Nonacetaminophen Pediatric Acute Liver Failure. *Journal of Pediatric Gastroenterology & Nutrition*.
- 15 2014;59(5):616-23.
- 16 32. Shalimar, Kedia S, Gunjan D, Sonika U, Mahapatra SJ, Nayak B, et al. Acute Liver Failure Due to Hepatitis E Virus
- 17 Infection Is Associated with Better Survival than Other Etiologies in Indian Patients. *Dig Dis Sci*. 2017;62(4):1058-66.
- 18 33. Silverio CE, Smithen-Romany CY, Hondal NI, Diaz HO, Castellanos MI, Sosa O. Acute liver failure in Cuban children.
- 19 *MEDICC Rev*. 2015;17(1):48-54.
- 20 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
- 21 in Serum Samples from Patients with Acute Liver Failure by Metagenomic Next-Generation Sequencing. *Clinical*
- 22 *Infectious Diseases*. 2017;65(9):1477-85.
- 23 35. Uddin Jamro BMC, S.; Mal Makheja, P.; Ahmed Soomro, A. Etiology, outcome and risk factors for fulminant hepatic
- 24 failure in children at a tertiary care hospital, Sukkur, Pakistan. *Rawal Medical Journal*. 2013;38(3):219-22.
- 25 36. Tsunoda T, Inui A, Iwasawa K, Oikawa M, Sogo T, Komatsu H, et al. Acute liver dysfunction not resulting from hepatitis
- 26 virus in immunocompetent children. *Pediatr Int*. 2017;59(5):551-6.
- 27 37. Zhao P, Wang CY, Liu WW, Wang X, Yu LM, Sun YR. Acute liver failure in Chinese children: a multicenter investigation.
- 28 *Hepatobiliary Pancreat Dis Int*. 2014;13(3):276-80.
- 29 38. Li SW, Zhao Q, Wu T, Chen S, Zhang J, Xia NS. The development of a recombinant hepatitis E vaccine HEV 239. *Hum*
- 30 *Vaccin Immunother*. 2015;11(4):908-14.
- 31 39. Wu X, Chen P, Lin H, Hao X, Liang Z. Hepatitis E virus: Current epidemiology and vaccine. *Human Vaccines and*
- 32 *Immunotherapeutics*. 2016;12(10):2603-10.
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

FIGURE LEGENDS

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	<i>Acute Liver Failure Study Group Germany</i> case definition: INR > 1.5 and encephalopathy of any grade. Pre-existing liver disease and systemic cause of liver failure were excluded

1								
2								
3								
4			To analyze clinical					
5			features, liver					Development of hepatic
6			function tests,					encephalopathy within 26
7	Bhatia et al., 2013 (17)	Prospective	hepatitis viral	India	Lower-	Jun-99	1-Jan	weeks of the first symptoms
8		cohort	markers and		middle			of acute hepatitis-like illness
9			clinical outcomes					without any history of
10			in patients with					underlying liver disease
11			ALF					
12								
13			To determine the					Development of
14			viral load of HEV					encephalopathy within 8
15			and its association					weeks of the onset of
16			with the disease					jaundice without any past
17	Borkakoti et al., 2013	Prospective	severity in patients	India	Lower-	6-Jan	11-Dec	history of chronic liver
18	(18)	cohort	with ALF in		middle			disease; diagnosed as a self-
19			comparison with					limiting disease and a serum
20			patients with ALF					aspartate aminotransferase
21			due to other					elevation of at least fivefold or
22			hepatides					clinical jaundice or both
23								
24								
25			To investigate the					Onset of coagulopathy and/or
26			etiology, outcomes					encephalopathy ≤ 4 weeks
27			and incidence of					after the onset of symptoms,
28	Bravo et al., 2012 (19)	Prospective &	AHF among	Philippines	Lower-	Jan-00	6-Dec	a prothrombin time > 2, an
29		retrospective	children 0-18		middle			increased bilirubin and
30		cohort	years old					evidence for liver failure
31								complicated by
32								encephalopathy
33								
34								<i>Mieli-Vergani</i> case definition:
35								a multisystem disorder in
36								which severe impairment of
37			To investigate the					liver function, with or without
38			impact of HAV UI					encephalopathy, occurs in
39	Cervio et al., 2011 (4)	Retrospective	on the trends in	Argentina	High	Mar-93	5-Jul	association with
40		cohort	the occurrence of					hepatocellular necrosis in a
41			FHF in children					patient with or without
42								recognized underlying chronic
43								liver disease (Cheeseman &
44								Mieli-Vergani, 2004)
45								
46								
47			To determine the					History of development of
48	Das et al., 2016 (20)	Prospective	profile of ALF	India	Lower-	7-Jan	15-Dec	encephalopathy within 8
49		cohort	etiologies		middle			weeks of disease onset
50								
51			To determine the					Elevated ALT levels or AST of
52			profile of Hepatitis					at least five-fold with clinical
53	Gupta et al., 2015 (21)	Retrospective	A, B, C and E as a	India	Lower-	11-Jan	14-Dec	jaundice and without evidence
54		cohort	cause of AHF in		middle			of chronic liver disease.
55			children in a					Patients who had INR > 1.5
56								
57								
58								
59								
60								

		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	<i>International Association for the Study of the Liver</i> 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	<i>International Association for the Study of Liver (IASL)</i> case definition: Occurrence of encephalopathy within 4 weeks from the onset of symptoms in the absence of preexisting liver disease

1								Evidence of liver damage in
2								the absence of prior known
3								chronic liver disease; altered
4								coagulation, expressed as PT
5								>15 s with encephalopathy; or
6								PT > 20 s with or without
7			To describe the					encephalopathy—all this
8	Silverio et al., 2015 (33)	Retrospective	clinical features of	Cuba	Upper-	5-Jan	11-Dec	within eight weeks of onset of
9		cohort	children treated for		middle			clinical symptoms
10			ALF					
11								
12								
13								
14			To investigate the					
15			causes of					
16	Somasekar et al., 2017	Retrospective	previously	United States	High	Jan-98	10-Dec	<i>United States Acute Liver</i>
17	(34)	cohort	diagnosed					<i>Failure Study Group</i> case
18			indeterminate					definition
19			cases ALF					
20								
21			To study the					Presence of acute liver failure
22			etiology, outcome					(coagulopathy PT > 20 s or
23	Uddin Jamro et al.,	Retrospective	and risk factors for	Pakistan	Lower-	7-Jul	12-Jun	INR > 2), HE without pre-
24	2013 (35)	cohort	FHF in children at		middle			existing liver disease, within 8
25			a tertiary care					weeks of the onset of clinical
26			hospital					liver disease
27								
28			To identify the					
29			roles of CMV, EBV					
30			and HHV in					
31	Tsunoda et al., 2017	Prospective	immunocompetent	Japan	High	7-Jan	13-Dec	Liver dysfunction with
32	(36)	cohort	children with acute					elevated AST and ALT > 30
33			liver failure not					IU/L
34			resulting from					
35			hepatitis virus					
36								
37								
38								Coagulopathy [PTA ≤40% or
39			To investigate					INR ≥ 1.5 excluding
40	Zhao et al., 2014 (37)	Retrospective	etiologies and	China	Middle	7-Jan	12-Dec	hematologic diseases] and
41		cohort	outcomes of					jaundice [Tbil ≥ 171 μmol/L]
42			children with ALF					within 4 weeks in a child
43								without pre-existing liver
44								diseases
45								
46	Abbreviations: ALF = acute liver failure; FHF = fulminant hepatic failure; AHF = acute hepatic failure; HEV = hepatitis E virus; CMV = cytomegalovirus; EBV							
47	= Epstein Barr virus; HHV = human herpesvirus; ELISA = enzyme-linked immunosorbent assay; INR = international normalized ratio; PT = prothrombin							
48	time; s = second; TSB = total serum bilirubin; HE = hepatic encephalopathy; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP =							
49	alkaline phosphatase; PTA = plasma thromboplastin antecedent							

Figure 1: Flow diagram for selection of studies

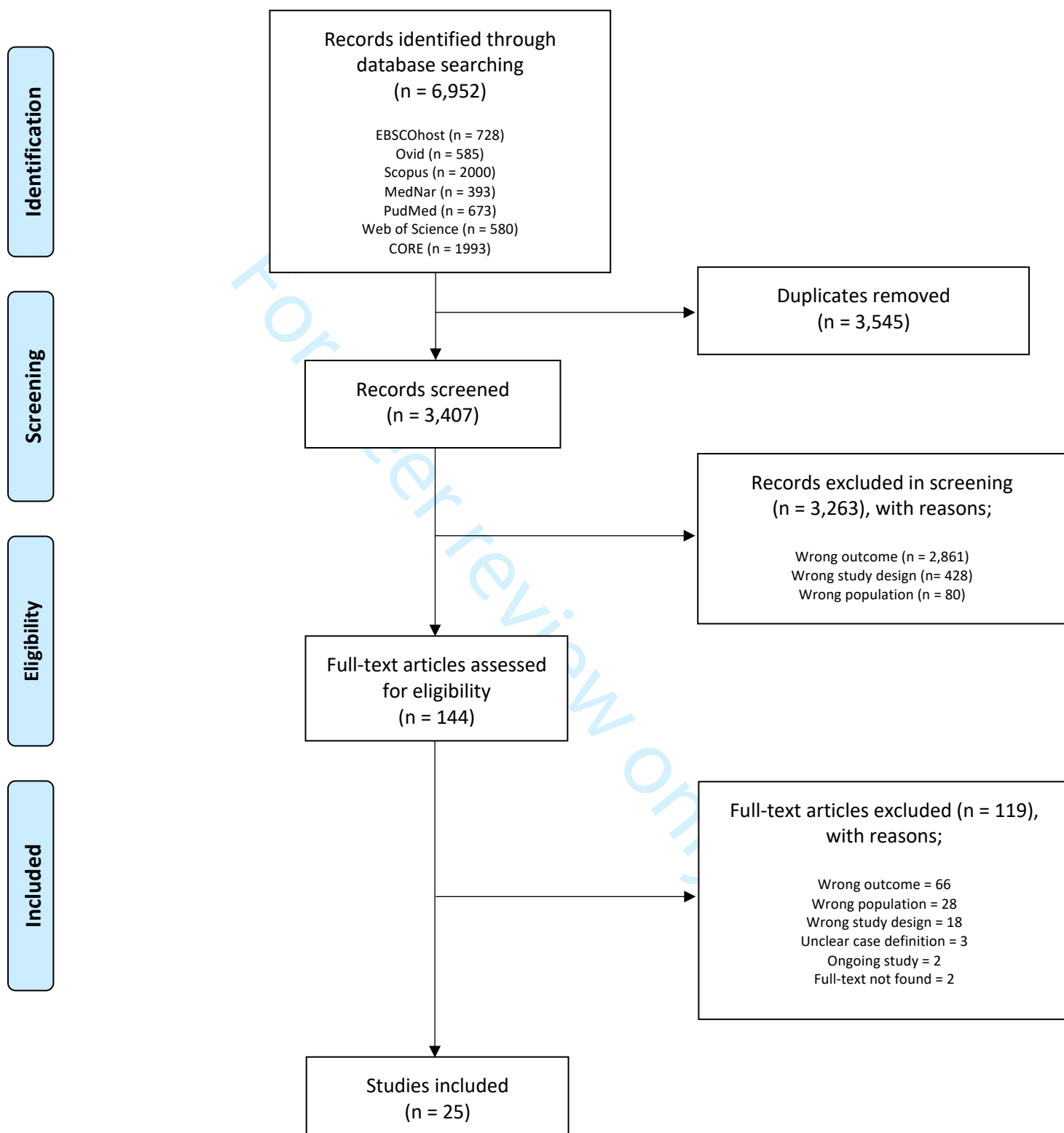


Figure 2: Prevalence of HAV-induced ALF by country HAV immunization status

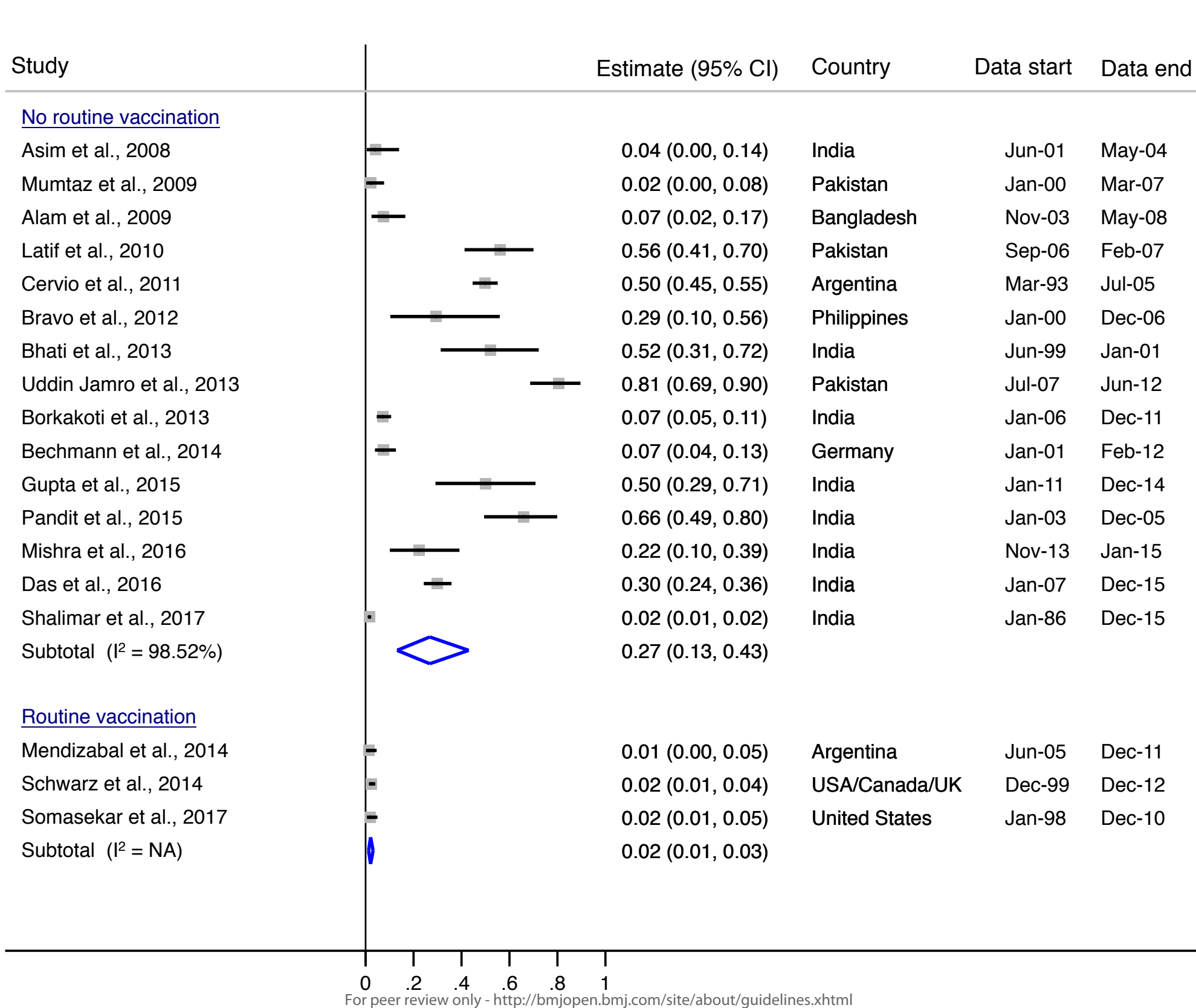
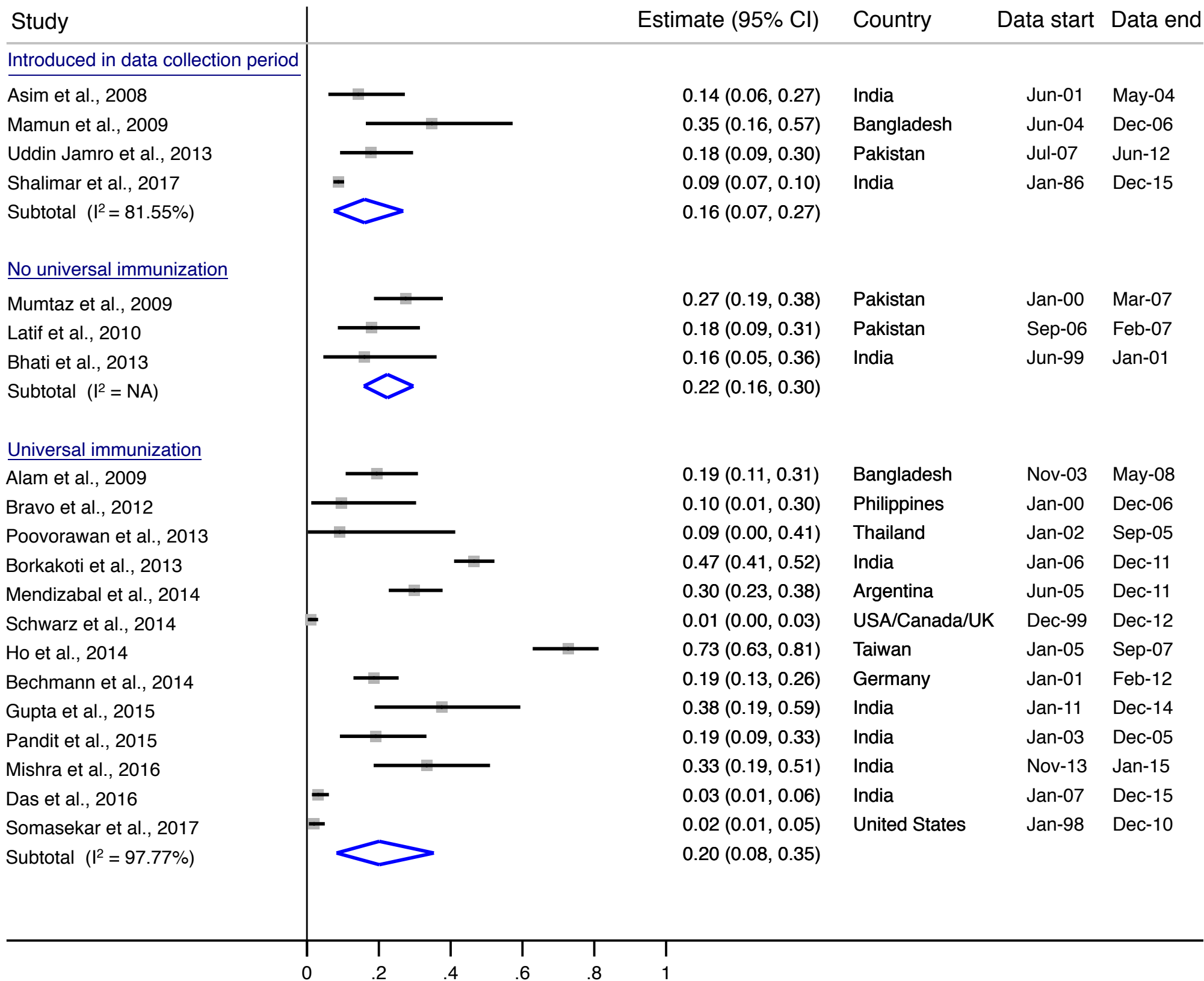
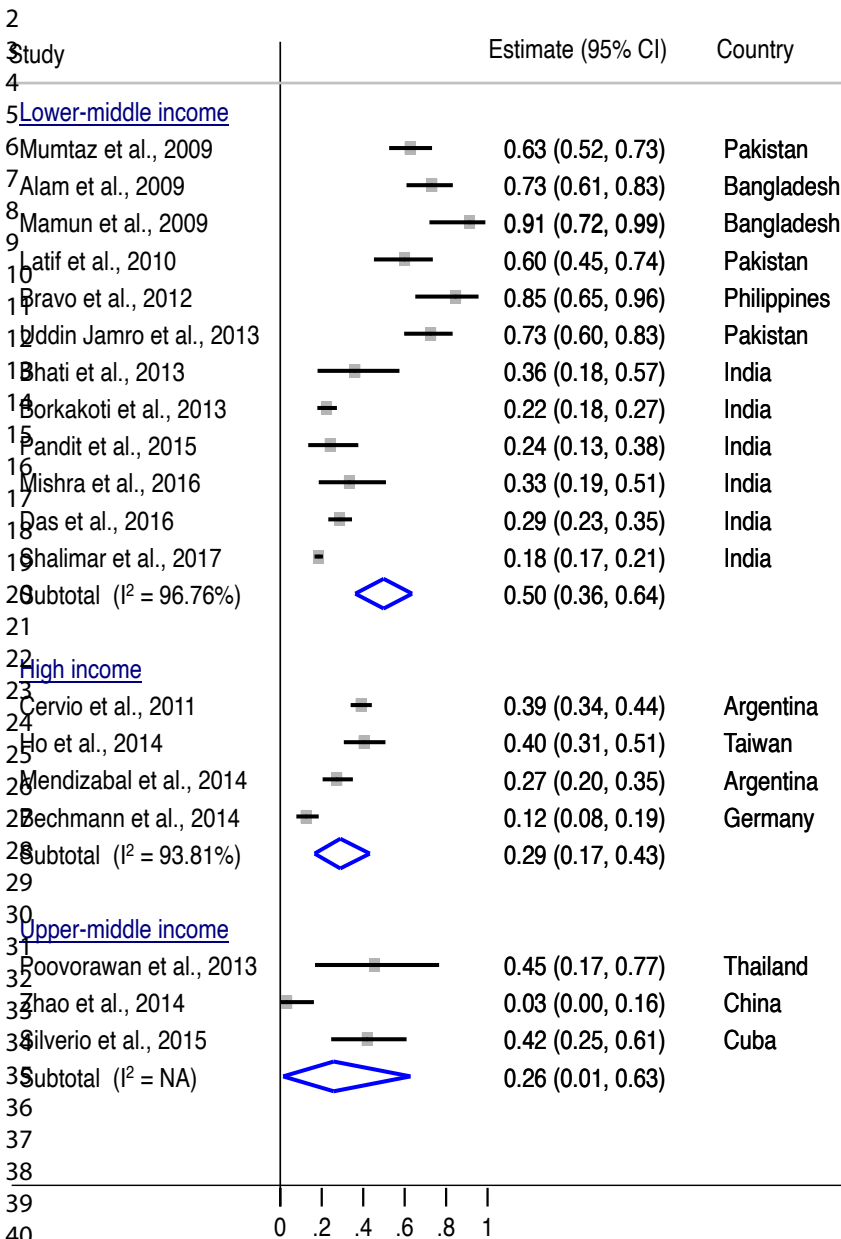


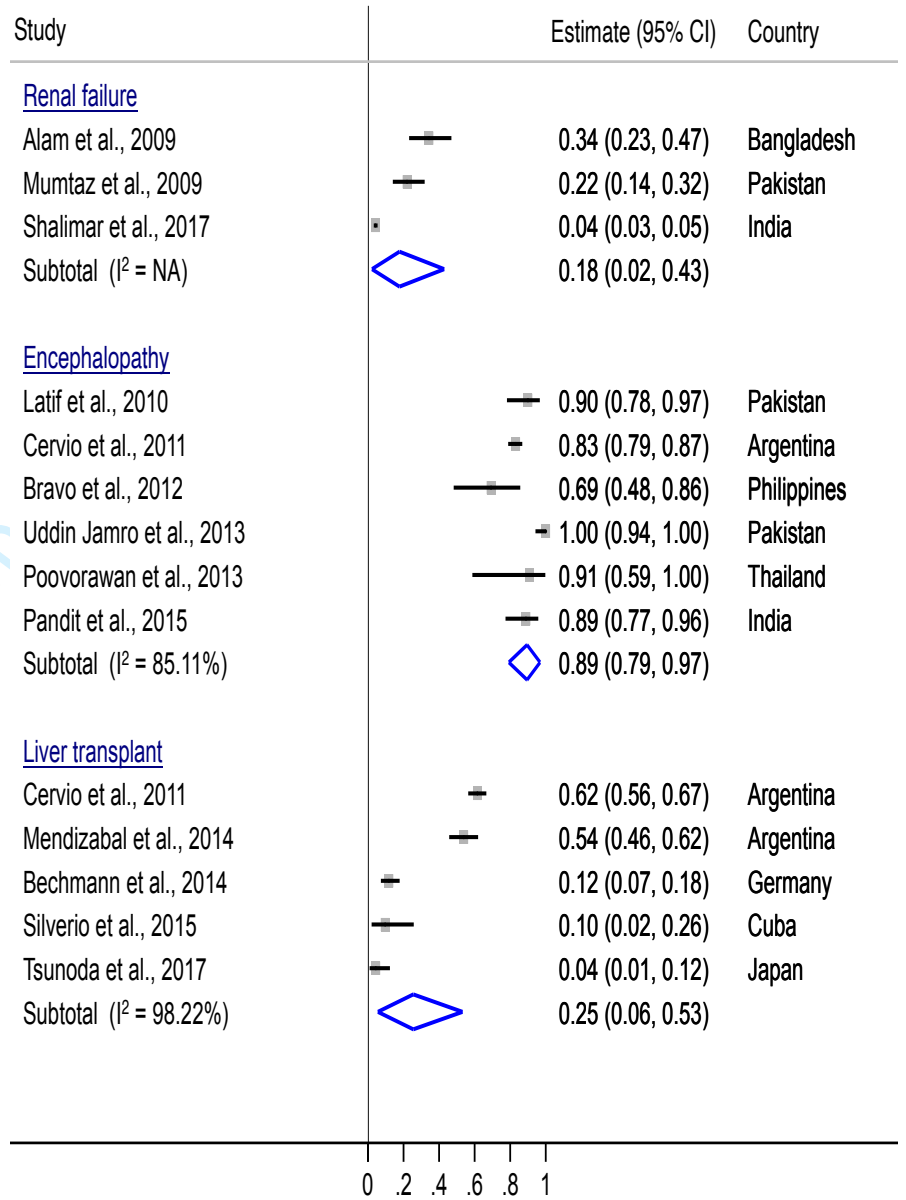
Figure 3: Prevalence of HBV-induced ALF by country HBV immunization status



A : Mortality rates associated with viral-induced ALF by country income status

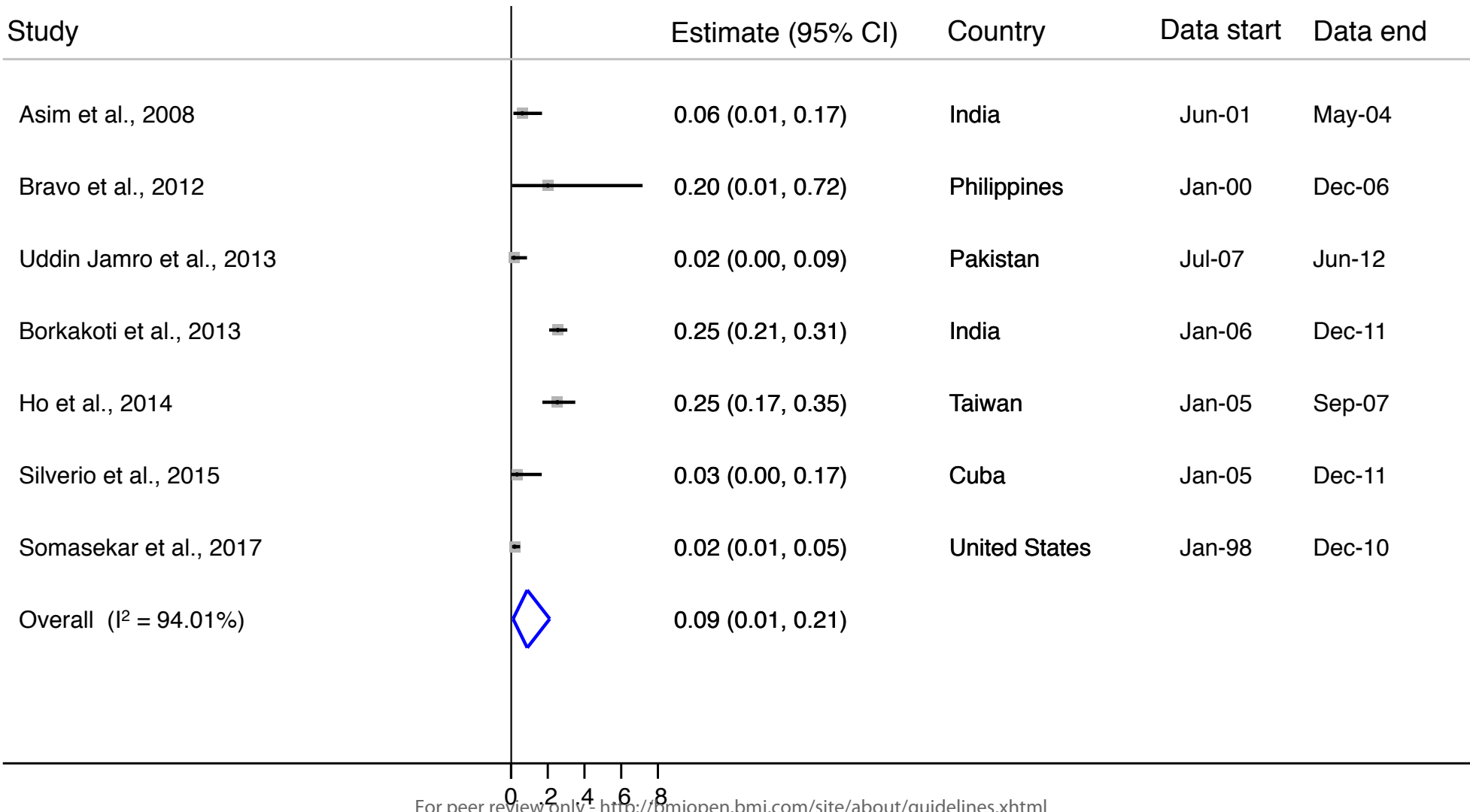


B : Prevalence of clinical outcomes associated with viral-induced ALF



Supplementary Figure 1: Prevalence of HCV-induced ALF

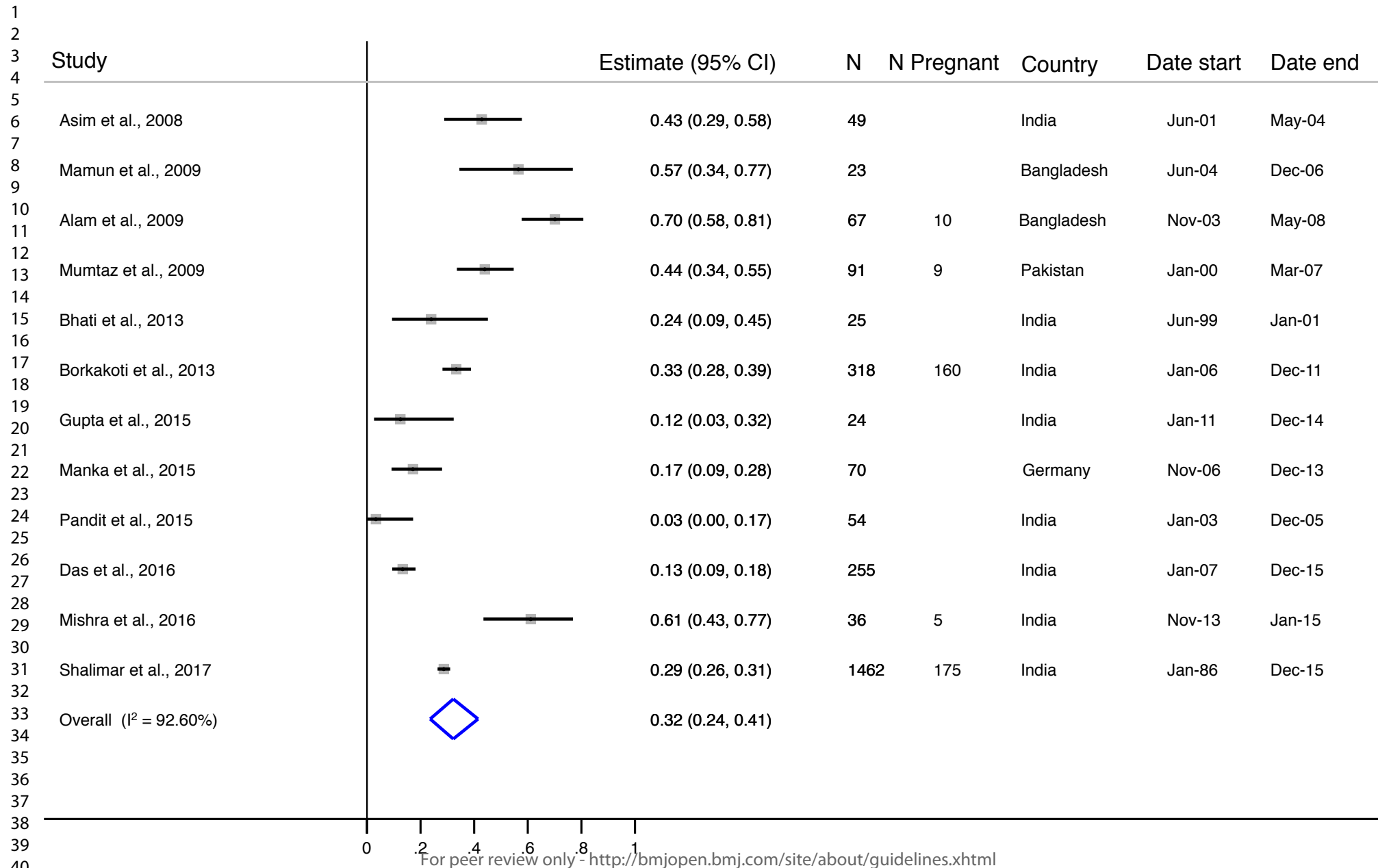
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Abbreviations: HCV = hepatitis C virus, ALF = acute liver failure, CI = confidence interval, I² = heterogeneity statistic

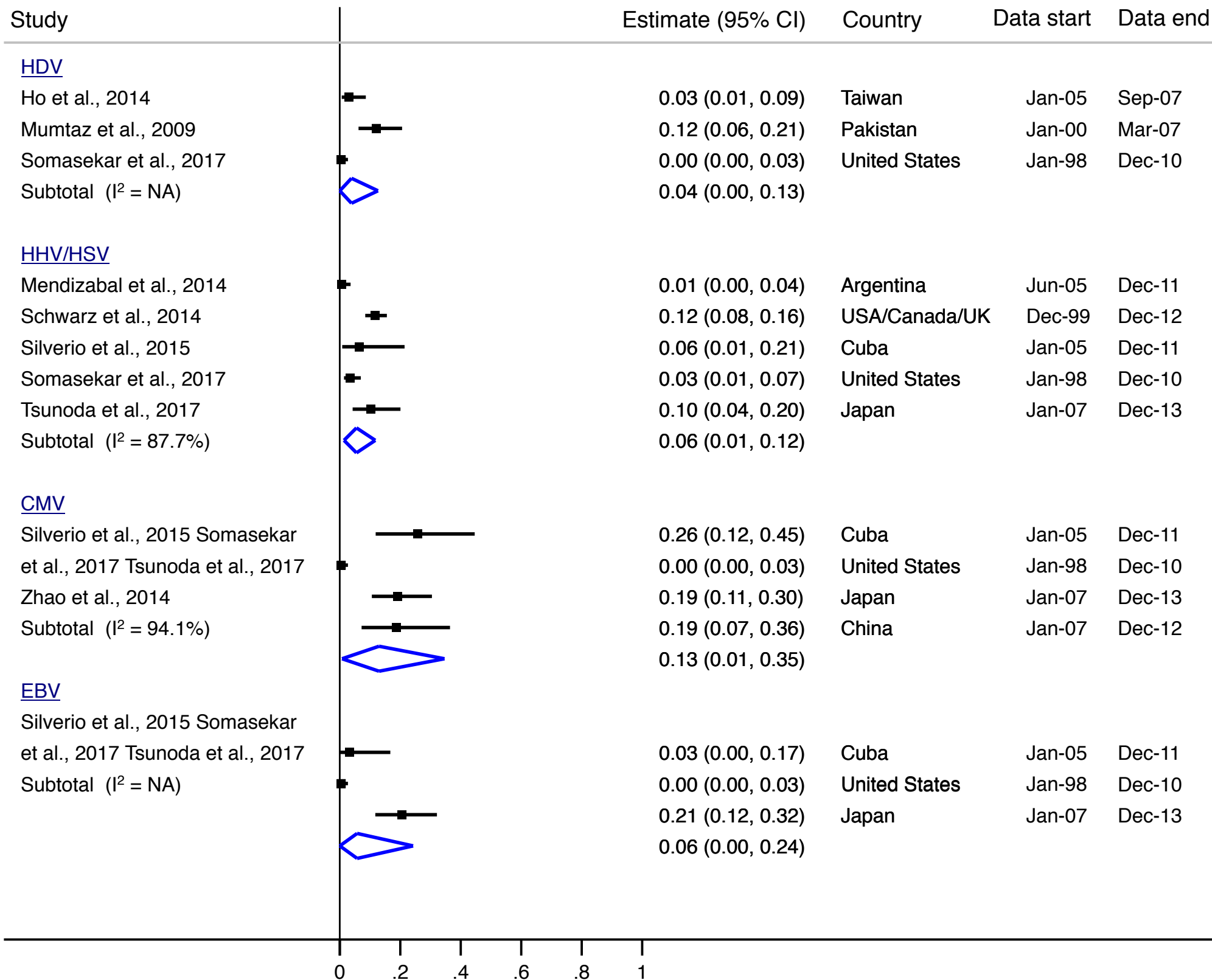
Supplementary Figure 2: Prevalence of HEV-induced ALF



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Abbreviations: HEV = hepatitis E virus, ALF = acute liver failure, CI = confidence interval, I² = heterogeneity statistic

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



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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	Represent ation of the national populatio n	Represent ation of target populatio n	Rand om select ion or censu s	Minim al likelih ood of non- respon se bias	Data collecte d directly from particip ants	Accept able case definiti on	Valid measure ment	Same mode of data collect ion	Appropri ate length	Appropri ate numerator (s) and denomina tor(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
Poorawan 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Uddin Jamro et al., 2013	Yes	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	Yes	9
Zhao et al., 2014	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
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 Hussey, Hannah; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health & Family Medicine Silal, Sheetal; University of Cape Town, Department of Statistical Sciences; University of Oxford, Nuffield Department of Medicine Goddard, Liz; University of Cape Town, Department of Paediatrics, Red Cross War Memorial Children's Hospital Setshedi, Mashiko; University of Cape Town, Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital Spearman, Wendy ; University of Cape Town, Department of Medicine, Division of Hepatology, Groote Schuur Hospital Hussey, Gregory; University of Cape Town 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 Kagina, Benjamin; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine 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 Initiative, School of Public Health and Family Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Epidemiology < INFECTIOUS DISEASES, Hepatology < INTERNAL MEDICINE, VIROLOGY

SCHOLARONE™
Manuscripts



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 Goddard⁵, Mashiko Setshedi⁶, C. Wendy Spearman⁷, Gregory D. Hussey^{1,8} Benjamin M. Kagina^{1,2} and Rudzani Muloiwa^{1,5}

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

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

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

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

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

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

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

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

⁵Department 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.

1
2
3 50 *Bernal et al. 2010* completed a review of the burden of acute and fulminant liver failure based on
4
5 51 literature published between 1997 and 2009. The review became the bases for guidelines for clinical
6
7 52 practice (5). In this systematic review, we assess whether data have changed following the Bernal
8
9 53 publication, and whether there is evidence to warrant a review of clinical practice.

10 11 54 **Objectives**

- 12 55 • To estimate the prevalence of hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus
13 56 (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex
14 57 virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19,
15 58 human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6),
16 59 cytomegalovirus (CMV), coxsackievirus (CA16) and/or adenovirus (HAdVs) among patients with
17 60 ALF.
- 18 61 • To estimate the mortality rate for cases of ALF following infection with HAV, HBV, HCV, HDV,
19 62 HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs
- 20 63 • To estimate the prevalence and incidence of liver transplantation for cases of ALF following
21 64 infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV,
22 65 HHV-6, CMV, CA16 and/or HAdVs

23 66 24 67 **Methods**

25 68 This systematic review was registered with PROSPERO (registration number CRD42017079730) and the
26 69 methods for its conduction have been published (11). The results of the review are reported using the
27 70 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines checklist.

28 71 29 72 **Study eligibility criteria**

30 73 Published cross-sectional, surveillance and cohort studies reporting the outcomes of interest in patients
31 74 with ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19,
32 75 HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs were eligible for inclusion in this study. Studies were
33 76 eligible for inclusion if they had clearly stated case definitions of viral-induced ALF and confirmed ALF
34 77 cases using both clinical and serological, molecular or culture diagnostic methods.

35 78 36 79 **Search strategy**

1
2
3 80 A combination of the following search terms (including the use of Medical Subject Headings (MESH))
4
5 81 was used and adapted for each of the relevant electronic databases: epidemiology, prevalence,
6
7 82 incidence, burden, mortality, morbidity, fulminant hepatic failure, fulminant liver failure, acute hepatic
8
9 83 failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV),
10
11 84 hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex virus-1 (HSV1),
12
13 85 herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses
14
15 86 (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), coxsackie virus
16
17 87 and adenovirus.

18 88
19 89 The following electronic databases were searched for relevant literature published from 2009 to 2019:
20 90 EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The search was run on 9 April 2019 and
21 91 updated via PubMed on 30 September 2019 with no new eligible studies to include.
22 92

23 93 **Data extraction**

24
25 94 Study characteristics and outcomes of interests were extracted from the included studies on a pre-
26
27 95 designed data extraction form by two independent reviewers (JP and HH). Prior to use by the two
28
29 96 reviewers, the reliability of the extraction form was assessed by piloting 10 randomly selected articles
30
31 97 that met the inclusion criteria. The study team resolved any disagreements in data extraction through
32
33 98 consensus in consultation with RM. In cases where studies were in German, HH provided translation. In
34
35 99 cases where studies were not available in English or German, google translate was used to translate the
36
37 100 article to English (12).

38 101 39 102 **Data synthesis and analysis**

40
41 103 A random-effects model was fitted to the study data as it included data taken from a series of
42
43 104 independently performed studies in different populations. We assessed heterogeneity by calculating I^2
44
45 105 statistics (threshold $I^2 > 40\%$). The values of I^2 were categorized for heterogeneity as follows: “not
46
47 106 important” ($\leq 40\%$), “moderate” ($> 40\%$ to $\leq 60\%$) and “considerable” ($> 60\%$ to $\leq 80\%$) and
48
49 107 “substantial” ($> 80\%$ to $\leq 100\%$). Where “not important” or “moderate” heterogeneity existed
50
51 108 between studies ($I^2 \leq 40\%$), pooled outcome measures were reported with 95% confidence intervals for
52
53 109 each respective outcome. Where “considerable” or “substantial” heterogeneity exists between studies
54
55 110 ($I^2 > 40\%$), forest plots and prevalence ranges calculated using the random-effects model were used to
56
57 111 narratively describe each outcome.

112 **Risk of bias assessment**

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

119 **Patient and public involvement**

120 This review was developed as part of an ongoing project by the research team that aims to generate
121 evidence to facilitate evidence-based decision-making of introducing routine hepatitis A vaccination in
122 South Africa. The findings of this review contribute to the knowledge base that aims to enhance global
123 vaccination strategies against viral-associated ALF. As this is a systematic review, no patient involvement
124 was required; however, it is hoped that the findings of this review will help to highlight the burden that
125 ALF places on populations without routine vaccination.

127 **Results**

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

139 **Vaccine-preventable viral-induced ALF**

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

1
2
3 144 combined of 2% (95% CI 1, 3) (**Figure 2**). In Argentina, the prevalence of HAV-induced ALF prior to
4
5 145 routine immunization was approximately 50% (95% CI 45, 55), compared to approximately 1% (95% CI 0,
6
7 146 5) after immunization was introduced. The point prevalence of HBV-induced ALF in countries without
8
9 147 universal HBV immunization at the time of data collection ranged from 16% to 27% with a combined of
10
11 148 22% (95% CI 16, 30) (**Figure 3**). The point prevalence of HBV-induced ALF in countries with universal HBV
12
13 149 immunization at the time of data collection ranged from 0% to 83% with a combined of 20% (95% CI = 8,
14
15 150 35).

151

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

153 The point prevalence of HCV-induced ALF ranged from 2% to 25% with a combined of 9% (95% CI = 1,
154 21) (**Supplementary Figure 1**). The point prevalence of HEV-induced ALF ranged from 3% to 70% with a
155 combined of 32% (95% CI 24, 41) (**Supplementary Figure 2**). The point prevalence of HDV-, HHV/HSV-,
156 CMV-, and EBV-induced ALF were estimated to have combined prevalences of 4% (95% CI 0, 13), 6%
157 (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%
158 (95% CI 0, 5), respectively (**Supplementary Figure 3**). Data was not available to estimate the burden of
159 ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and/or HAdVs as outlined per the published
160 protocol (11).

161

162 **Outcomes of viral-induced ALF**

163 The narratively reported outcomes of viral-induced ALF were found to be severe. The mortality rates
164 associated with viral-induced ALF in lower-middle income countries ranged from 18% to 91% with a
165 combined mortality rate of 50% (95% CI 36, 64) (**Figure 4A**). The mortality rates associated with viral-
166 induced ALF in upper-middle income countries ranged 3% to 45% with a combined mortality rate of 26%
167 (95% CI 1, 63) (**Figure 4A**). The mortality rates associated with viral-induced ALF in high income countries
168 ranged from 12% to 40% with a combined mortality rate of 29% (95% CI 17, 43) (**Figure 4A**). The rate of
169 encephalopathy associated with viral-induced ALF cases in children ranged from 69% to 100% with a
170 combined rate of 89% (95% CI 79, 97) (**Figure 4B**). The need for liver transplantation with viral-
171 associated ALF ranged from 4% to 62% with a combined rate of 25% (95% CI 6, 53) (**Figure 4B**). The need
172 for renal transplant in viral-associated ALF cases ranged from 4% to 34% with a combined rate of 18%
173 (95% CI 2, 43) (**Figure 4B**).

174

175 **Methodological quality**

1
2
3 176 Risk of bias scores were assigned by two reviewers (JP and HH) and are described in **Supplementary**
4
5 177 **Table 1**. Overall, a majority of the included studies were judged as having ‘low risk’ of bias. Only one
6
7 178 included study was judged as having ‘moderate risk’ of bias due to lack of clarity around the
8
9 179 representativeness of the study population to the national population, methods of participant selection
10
11 180 and methods employed to reduce the likelihood of non-response.
12

181

13 182 **Discussion**

14
15 183 This systematic review estimated the burden of ALF following infection with HAV, HBV, HCV, HEV,
16
17 184 HSV/HHV, CMV, EBV, and parvo-virus B19. The prevalence of HAV-induced ALF is markedly lower in
18
19 185 countries with routine HAV immunization while HEV was the most common etiological cause of viral-
20
21 186 induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by
22
23 187 high fatality rates, which seem to increase with poor economic status of the studied countries.
24

188

25 189 The estimated prevalence of HAV-induced ALF in countries with routine HAV immunization was
26
27 190 markedly lower than the estimated prevalence in countries without routine HAV immunization. When
28
29 191 looking at countries with data before and after the introduction of routine HAV immunization, the
30
31 192 reduction of HAV-induced ALF due to vaccination is further highlighted. The combined prevalence of
32
33 193 HBV-induced ALF was the same in settings with or without universal HBV immunization. Countries
34
35 194 without universal HBV immunization programs are likely to have weak healthcare systems; thus, the
36
37 195 reported prevalence of HBV-induced ALF is assumed to be an underestimate of the true burden in these
38
39 196 populations due to weak routine testing and reporting systems. Currently, there is one HEV vaccine
40
41 197 (Hecolin) licensed in China that has shown promise with a high degree of efficacy in preventing HEV
42
43 198 genotype IV infection in healthy individuals 16 to 65 years (15). Further exploration of the efficacy of this
44
45 199 vaccine for prevention of infection with genotypes I and II in different populations should to explore it’s
46
47 200 application in different countries and HEV endemicity settings (16).

201

48
49 202 This review estimated the mortality rate for viral-induced ALF to be approximately 50% in low- and
50
51 203 middle- income countries (LMICs) and less than 30% in upper-middle- and high-income countries.
52
53 204 Previous studies have estimated that mortality rates associated with ALF vary between 60% and 80%,
54
55 205 depending on the disease etiology as well as a patient’s access to care. Our review shows that although
56
57 206 viral-induced ALF still carries a significant mortality, though possibly lower than that reported for other
58
59 207 ALF etiologies (5, 6). Mortality data largely comes from hospitals with the capacity to diagnose viral-

7

1
2
3 208 induced ALF, thus deaths outside of the hospital system or ALF deaths without virological testing may
4
5 209 not be captured in these mortality estimates. Liver transplantation is required by approximately 25% of
6
7 210 viral-induced ALF cases and approximately 18% of viral-induced ALF cases required renal
8
9 211 transplantation, globally. In addition to general lack of resources for transplantation, a significant
10
11 212 proportion of potential candidates have contraindications to transplant related to poor socioeconomic
12
13 213 status in LMICs. The transplant data included in this review may only reflect successful and unsuccessful
14
15 214 transplants, not those that were needed but not carried out due to resource constraints or
16
17 215 contraindications.

18
19 216
20 217 This review is limited by lack of data for some of the viral etiologies of ALF including for VZV, HPIVs, YFV,
21
22 218 CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced
23
24 219 ALF. Additionally, we believe that our findings underestimate the global burden of viral-induced ALF as
25
26 220 some important causes of ALF (e.g. HSV/HHV) are believed to be underrecognized as they require PCR
27
28 221 testing for diagnosis. The included studies also used varying methods of virus detection including
29
30 222 serology and molecular tests which further added to the heterogeneity in the results of our review. This
31
32 223 is a well-recognized limitation in studies of ALF where diagnostics are often limited by cost in under-
33
34 224 resourced regions where viral causes of ALF are more prevalent. The limited availability of data,
35
36 225 including lack of same country data on burden of disease before and after introduction of immunization,
37
38 226 hindered most of the planned sub-group analyses outlined in the study protocol. Where data were
39
40 227 available, high heterogeneity of the data led to planned meta-analyses and meta-regression analyses
41
42 228 not being possible. Lastly, the diversity of viruses attributable to ALF cases led to low statistical power in
43
44 229 meta-analyses conducted.

45
46 230
47 231 Future research should assess the burden of viral-induced ALF following infection with HDV, VZV, HPIVS,
48
49 232 YFV, CA16 and HAdVs. Collectively, high-quality data on all viral etiologies of ALF would allow for better
50
51 233 pooling of results. The review team encourages future studies to incorporate health economic estimates
52
53 234 and mathematical modelling where data permits to assist health policy decision-makers to better design
54
55 235 strategies for the prevention and management of viral-induced ALF. Epidemiological-economic
56
57 236 modelling of immunization against HAV, HBV and HEV may well show that introduction of vaccination
58
59 237 could lead to future cost savings in the long run due to prevented medical care and liver failure.

60 238

239 **Conclusions**

1
2
3 240 We successfully addressed the aim of the study although data on VZV, HPIVs, YFV, CA16 and/or HAdVs
4
5 241 were missing. Notwithstanding the noted limitations, it is clear that HAV, HBV and HEV – vaccine-
6
7 242 preventable ALF etiologies – account for a large proportion of ALF (approximately 21%, 20%, 32% of
8
9 243 viral-induced ALF cases, respectively). The burden of ALF that is associated with vaccine-preventable ALF
10
11 244 etiologies should be used in conjunction with other available key evidence to inform practice and
12
13 245 policies on immunization, particularly in LMICs. A majority of LMICs have established universal
14
15 246 vaccination against HBV. The World Health Organization has recently recommended the introduction of
16
17 247 an HBV birth dose which is aimed at elimination of the virus and, if successful, will subsequently reduce
18
19 248 the burden of HBV-induced ALF. Routine HAV immunization in LMICs, however, are lacking. More data is
20
21 249 urgently needed to guide routine use of the vaccine in prevention of morbidity and mortality caused by
22
23 250 the virus. Lastly, further applicability of HEV vaccines should be explored, especially in LMICs where
24
25 251 resources for managing viral-induced ALF are glaringly lacking.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **253 Contributors**

4
5 254 JP, GDH, BK and RM conceived this study. JP implemented the review under the supervision of RM. JP
6 255 and HSH performed the study search, screening and extraction of data under the guidance of RM. GDH
7
8 256 and BK provided methodological expertise for this review. SS, LG, MS, and WS provided content
9
10 257 expertise for this review and all authors will provided comments on the final manuscript before
11
12 258 publication. JP is the guarantor of this review.

13 **259 Funding**

14
15 260 This research received no specific grant from any funding agency in the public, commercial or not-for-
16
17 261 profit sectors. The Vaccines for Africa Initiative (VACFA) has funded the costs associated with the
18
19 262 research and dissemination of the results, including publications.

20 **263 Competing interests**

21
22 264 None declared.

23 **265 Data availability**

24
25 266 All data were taken from published articles available in the public domain.

26
27 **267 Patient consent for publication**

28
29 268 Not required.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 agreement. *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 AI 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.

- 1
2
3 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.
- 4 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.
- 5 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.
- 6 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.
- 7 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.
- 8 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.
- 9 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.
- 10 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.
- 11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

FIGURE LEGENDS

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	<i>Acute Liver Failure Study Group Germany</i> 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

1								
2								
3								
4								Onset of coagulopathy and/or
5								encephalopathy ≤ 4 weeks
6								after the onset of symptoms,
7	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	a prothrombin time > 2 , an increased bilirubin and evidence for liver failure complicated by encephalopathy
11								
12								
13								<i>Mieli-Vergani</i> case definition:
14								a multisystem disorder in
15								which severe impairment of
16								liver function, with or without
17								encephalopathy, occurs in
18	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	association with hepatocellular necrosis in a patient with or without recognized underlying chronic liver disease (Cheeseman & Mieli-Vergani, 2004)
22								
23								
24								
25								
26	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
27								
28								
29								
30								Elevated ALT levels or AST of
31								at least five-fold with clinical
32								jaundice and without evidence
33	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	of chronic liver disease. Patients who had INR > 1.5 with encephalopathy or INR > 2 without encephalopathy
34								
35								
36								
37								
38								
39								International Classification of
40	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	Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 570.0
41								
42								
43								
44								
45								Development of
46								encephalopathy within 8
47								weeks of the onset of
48	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	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
49								
50								
51								
52								
53								
54								
55								
56								
57								
58								
59								
60								

1								
2								
3								
4								Previously healthy patients
5								who presented with severe
6								impairment of hepato-cellular
7	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	function, i.e. encephalopathy, coagulopathy, and jaundice, within six months of onset of symptoms
8								
9								
10								
11								
12								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
13	Manka et al., 2015 (28)	Retrospective cohort	To investigate the causes of previously diagnosed indeterminate cases ALF	Germany	High	6-Nov	13-Dec	
14								
15								
16								
17								
18								
19								
20								
21								
22								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
23	Mendizabal et al., 2014 (29)	Retrospective cohort	To determine the causes and short-term outcomes of ALF	Argentina	High	5-Jun	11-Dec	
24								
25								
26								
27								
28								
29								
30								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
31	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	
32								
33								
34								
35								
36								
37								
38								
39								
40	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
41								
42								
43								
44								
45								
46								
47								
48								
49								Onset of encephalopathy \leq 28 days after the onset of symptoms with INR > 2 and increased bilirubin complicated by encephalopathy in patients
50	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	
51								
52								
53								
54								
55								
56								
57								
58								
59								
60								

							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	<i>International Association for the Study of the Liver</i> 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 \geq 15 s or INR \geq 1.5 in the presence of clinical HE or a PT \geq 20 s or INR \geq 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	<i>International Association for the Study of Liver</i> (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	<i>United States Acute Liver Failure Study Group</i> 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 \leq 40% or INR \geq 1.5 excluding hematologic diseases] and jaundice [Tbil \geq 171 μ mol/L] within 4 weeks in a child without pre-existing liver diseases
<p>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</p>								

Figure 1: Flow diagram for selection of studies

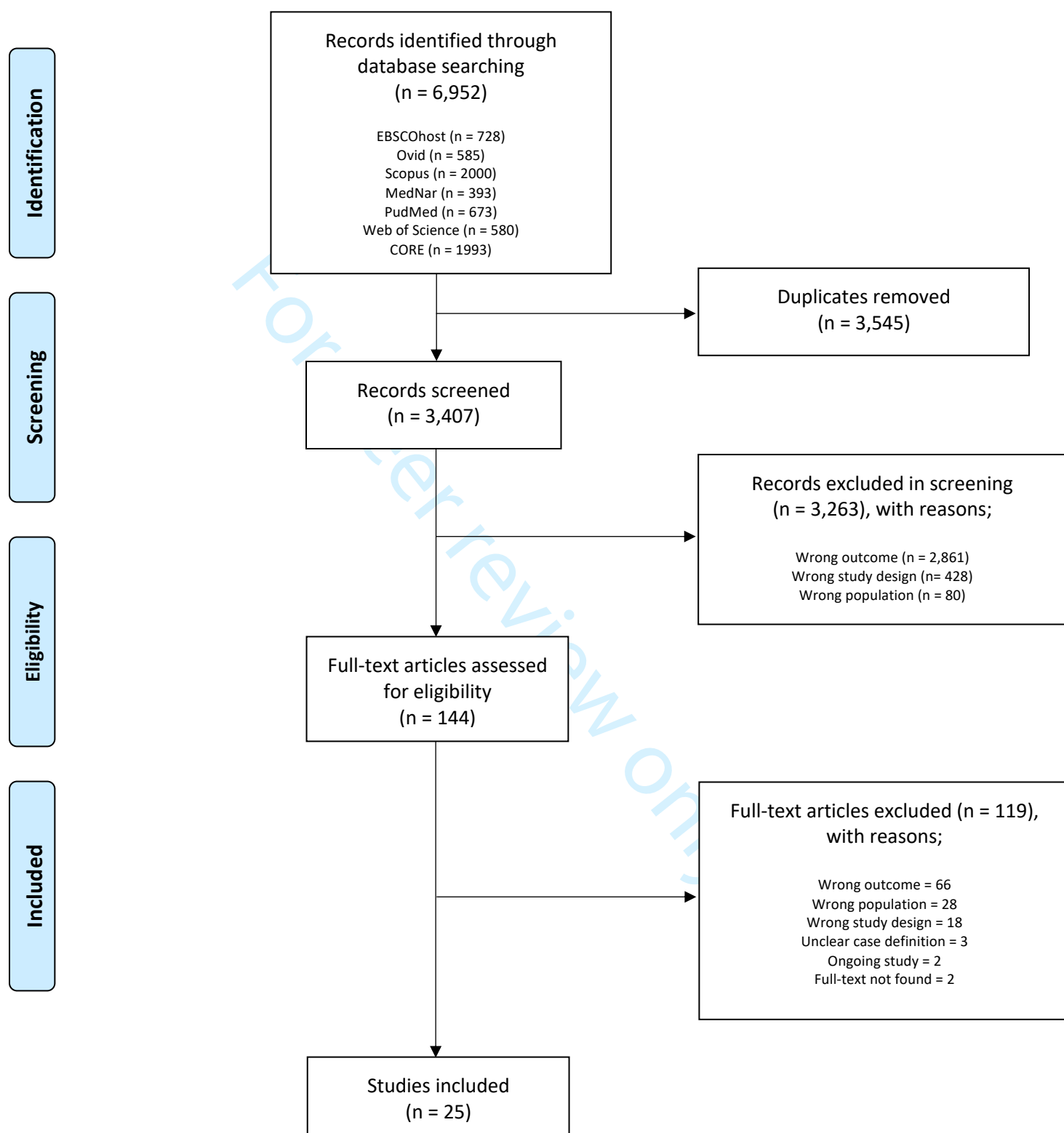


Figure 2: Prevalence of HAV-induced ALF by country HAV immunization status

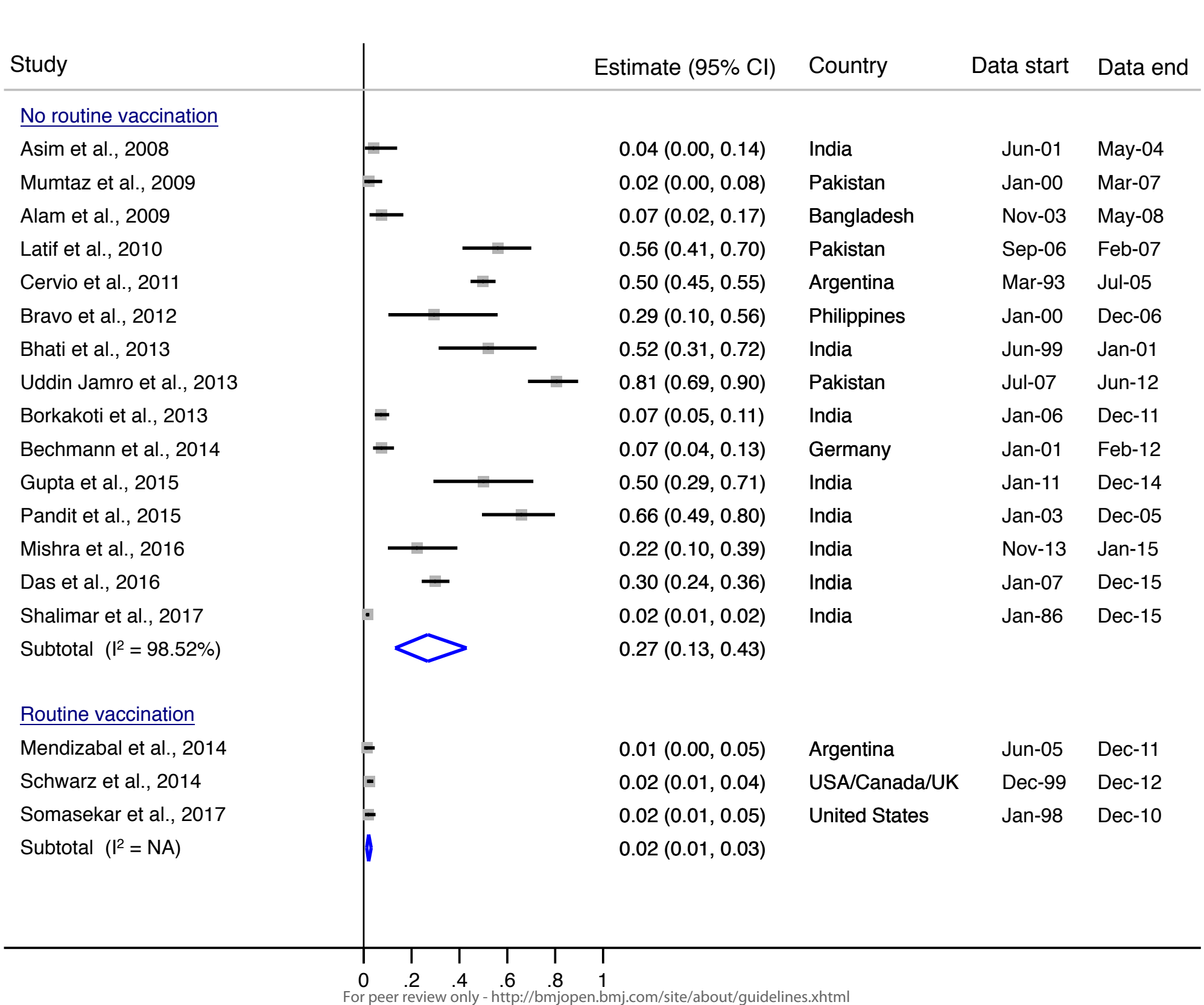


Figure 3: Prevalence of HBV-induced ALF by country HBV immunization status

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56

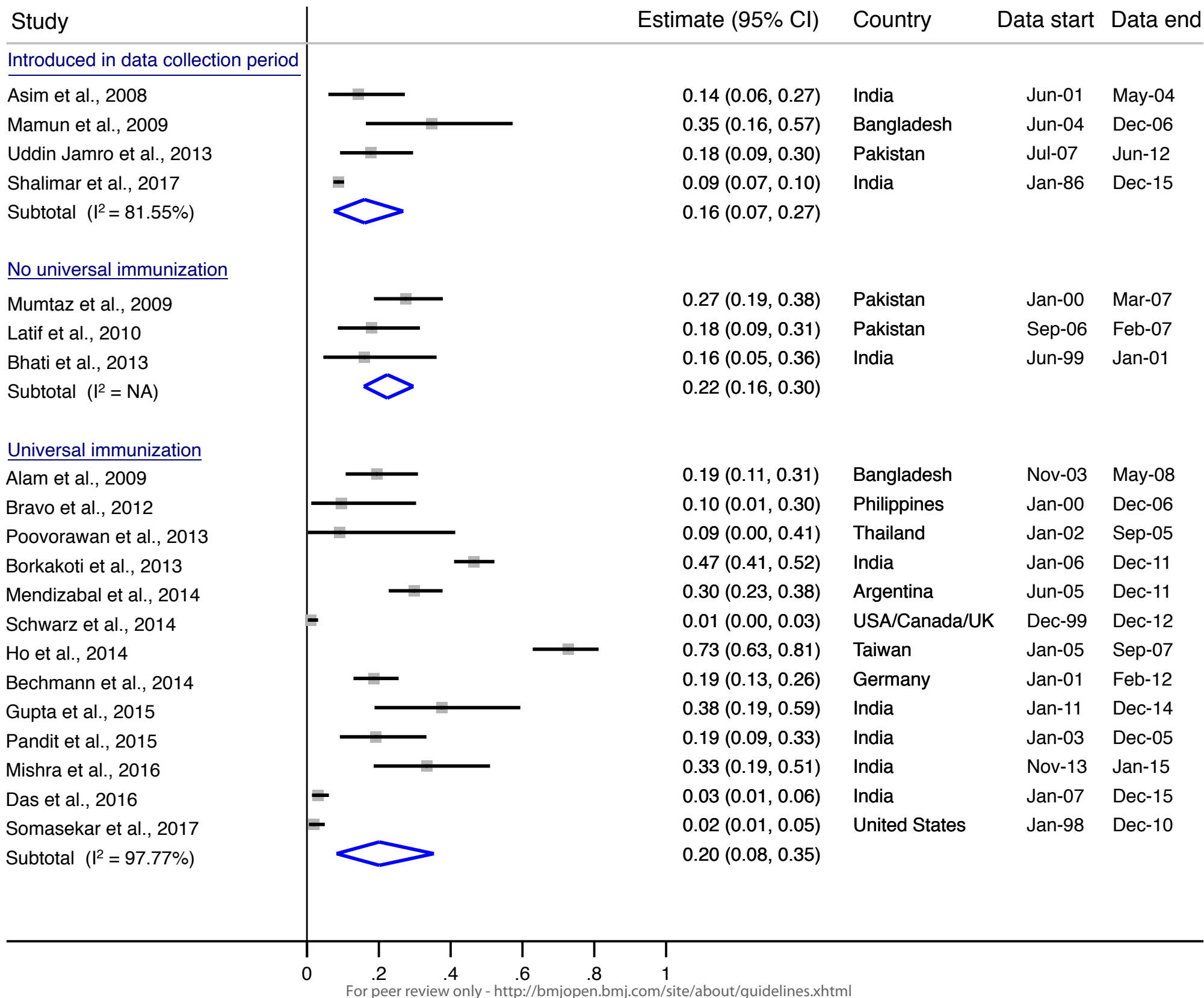
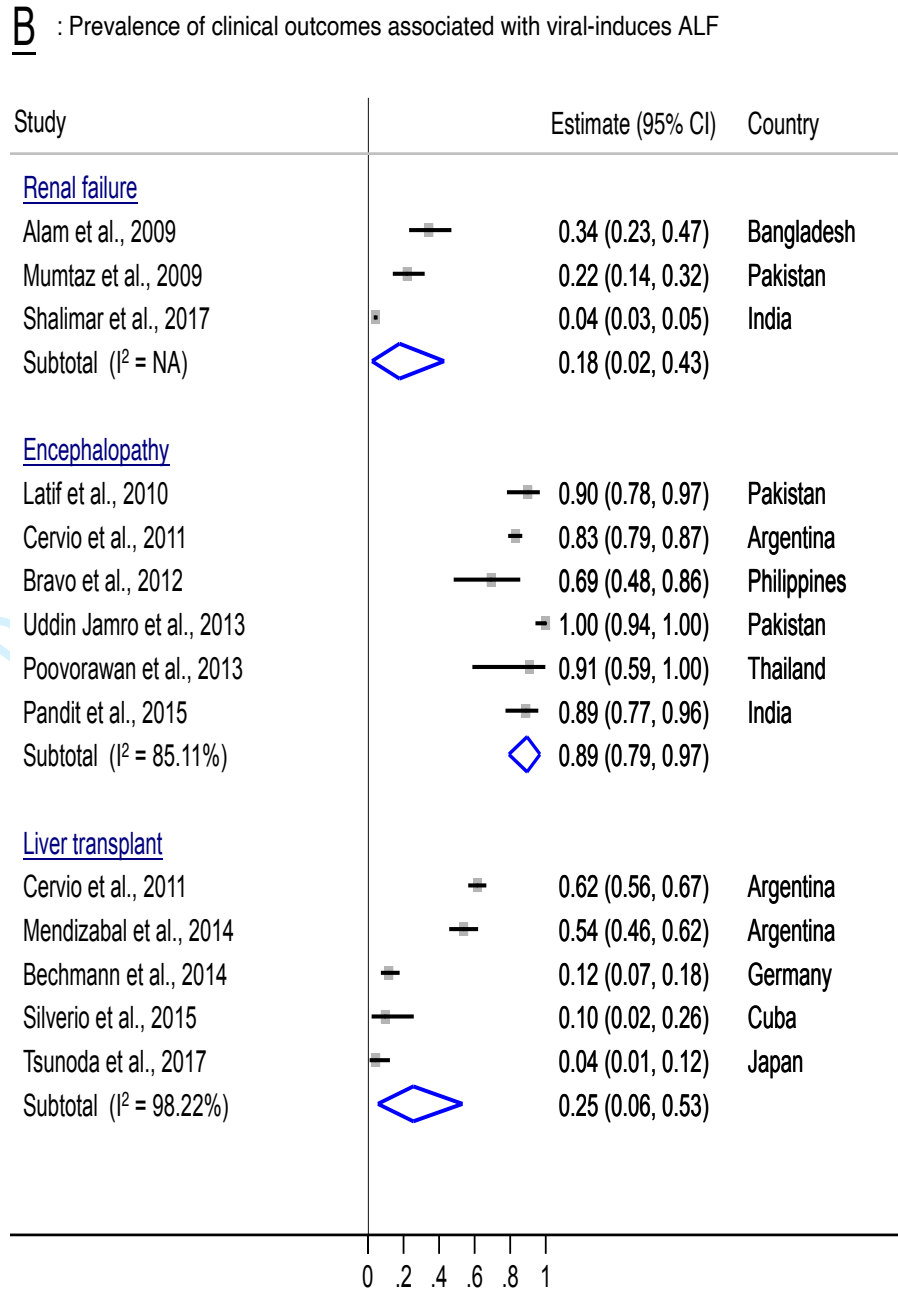
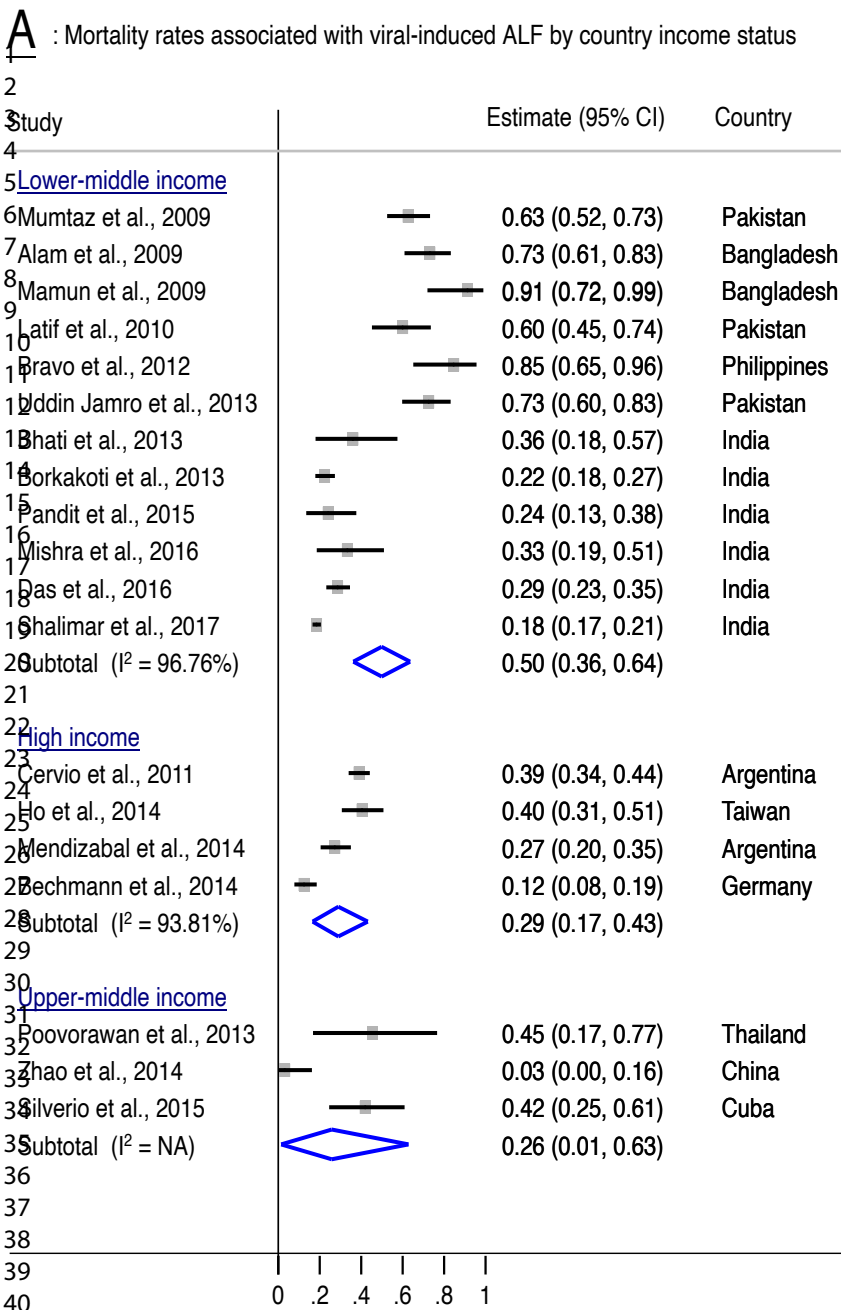
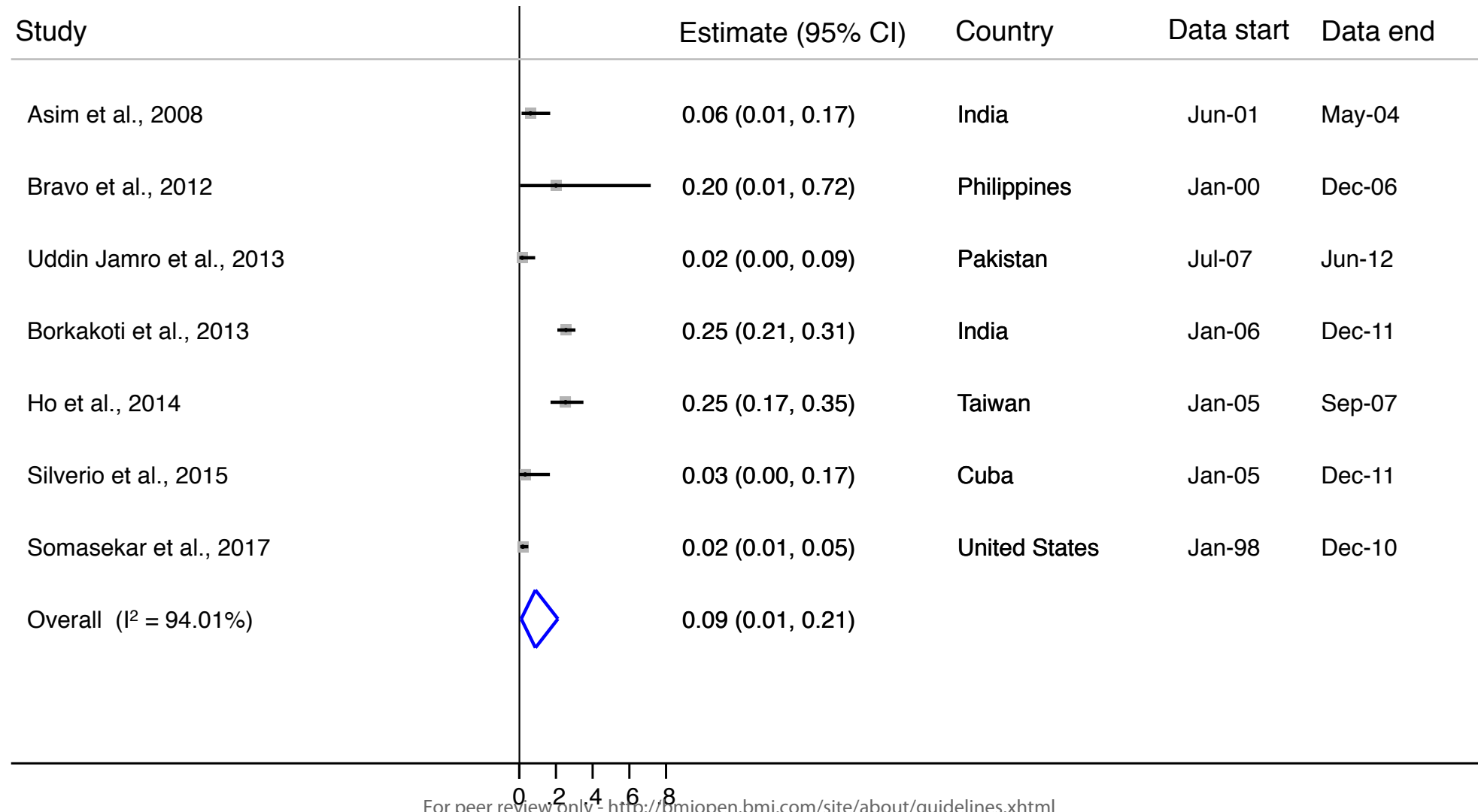


Figure 4: Prevalence of outcomes associated with viral-induced ALF



Supplementary Figure 1: Prevalence of HCV-induced ALF

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

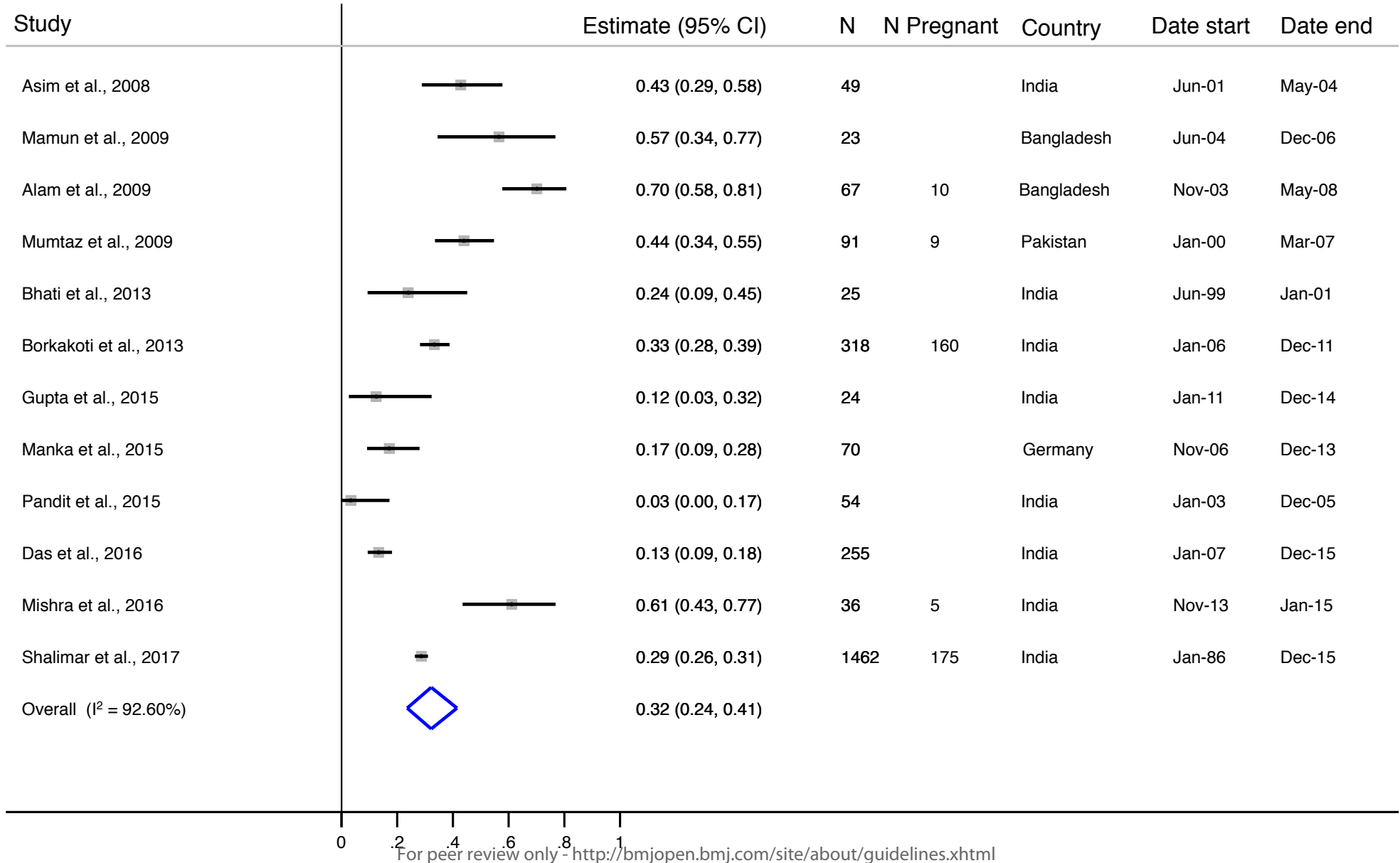


For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Abbreviations: HCV = hepatitis C virus, ALF = acute liver failure, CI = confidence interval, I² = heterogeneity statistic

Supplementary Figure 2: Prevalence of HEV-induced ALF

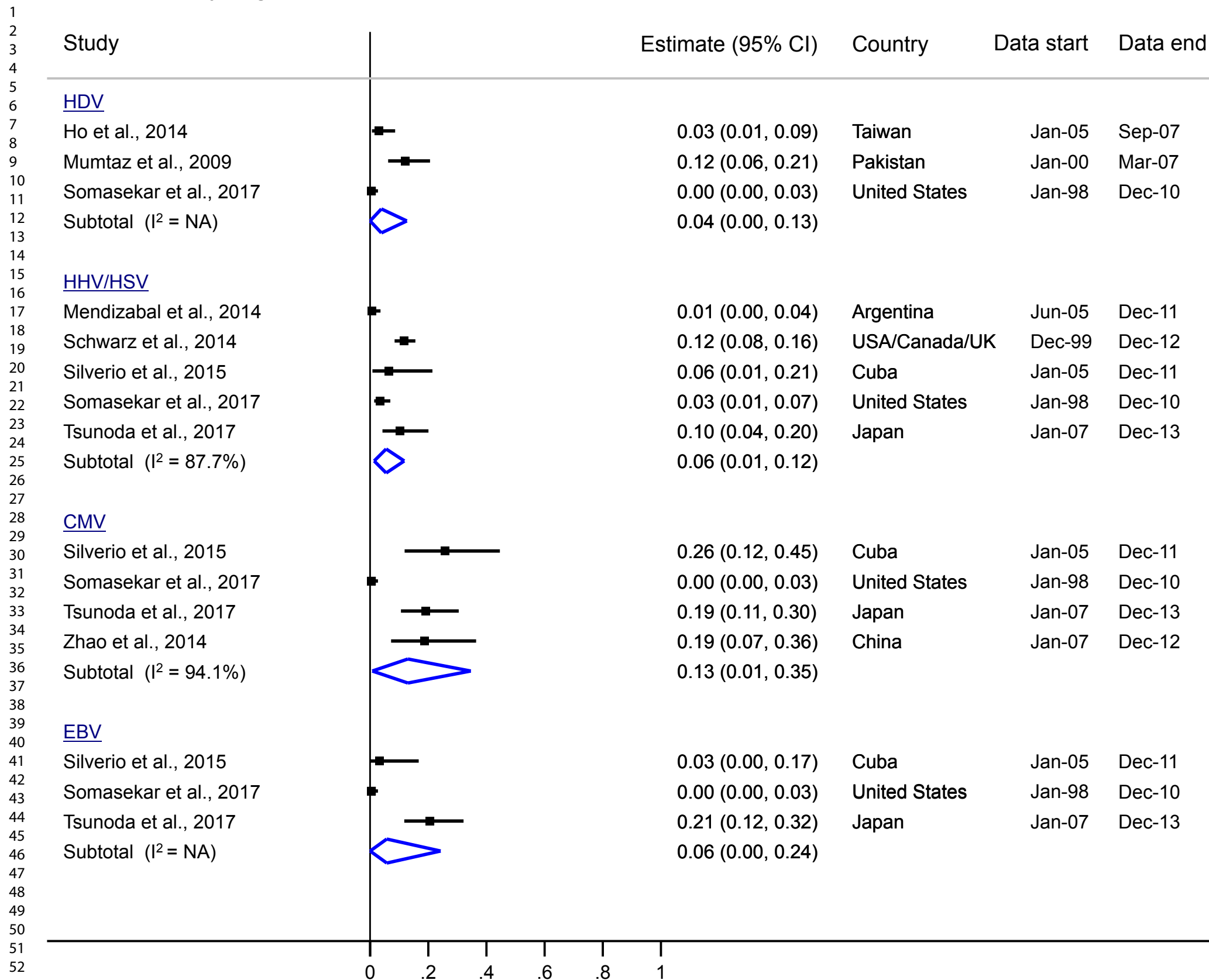
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Abbreviations: HEV = hepatitis E virus, ALF = acute liver failure, CI = confidence interval, I² = heterogeneity statistic

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



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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	Represent ation of the national populatio n	Represent ation of target populatio n	Rand om select ion or censu s	Minim al likelih ood of non- respon se bias	Data collecte d directly from particip ants	Accept able case definiti on	Valid measure ment	Same mode of data collect ion	Appropri ate length	Appropri ate numerator (s) and denomina tor(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	Yes	10
Tsunoda et al., 2017	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Zhao et al., 2014	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8

For peer review only



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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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
----------------------	----	---	---

Page 1 of 2

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



PRISMA 2009 Checklist

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47

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

Page 2 of 2

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
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 Hussey, Hannah; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health & Family Medicine Silal, Sheetal; University of Cape Town, Department of Statistical Sciences; University of Oxford, Nuffield Department of Medicine Goddard, Liz; University of Cape Town, Department of Paediatrics, Red Cross War Memorial Children's Hospital Setshedi, Mashiko; University of Cape Town, Department of Medicine, Division of Gastroenterology, Groote Schuur Hospital Spearman, Wendy ; University of Cape Town, Department of Medicine, Division of Hepatology, Groote Schuur Hospital Hussey, Gregory; University of Cape Town 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 Kagina, Benjamin; University of Cape Town Faculty of Health Sciences, Vaccines for Africa Initiative, School of Public Health and Family Medicine Muloiswa, 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 Initiative, School of Public Health and Family Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Epidemiology < INFECTIOUS DISEASES, Hepatology < INTERNAL MEDICINE, VIROLOGY

SCHOLARONE™
Manuscripts



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 Goddard⁵, Mashiko Setshedi⁶, C. Wendy Spearman⁷, Gregory D. Hussey^{1,8} Benjamin M. Kagina^{1,2} and Rudzani Muloiwa^{1,5}

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

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

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

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

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

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

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

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

⁵Department 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.

23

1

1
2
3 24 **MANUSCRIPT**
4 25
5 26

6 **Background**

7 27 Acute liver failure (ALF) refers to the development of encephalopathy and synthetic function impairment
8
9 28 following acute liver injury in an individual without pre-existing liver disease (1). The presence of
10
11 29 encephalopathy is not required to define ALF in paediatrics, but is an essential component of the
12
13 30 definition in adults (1). Possible causes of ALF include viral infections, drugs and toxins, pregnancy
14
15 31 related liver diseases, vascular causes and/or malignancies. Acute viral hepatitis has been identified as
16
17 32 the most common cause of ALF among all ages in Asia and Africa and one of the most common causes of
18
19 33 ALF in children in Asia and South America (2, 3). The incidence of viral-induced ALF has substantially
20
21 34 declined in Europe following the introduction of universal immunization against the hepatitis B virus
22
23 35 (HBV), with only 19% of all ALF cases now attributable to viral infection in the European population (4).
24
25 36 The introduction of routine immunization against the hepatitis A virus (HAV) in Argentina has reduced
26
27 37 the number of hepatitis A induced ALF cases by more than 25% (4).

28
29 38 Fatality rates associated with ALF vary between 60% and 80%, depending on the disease etiology as well
30
31 39 as a patient's access to care (5, 6). Liver transplantation plays a central role in the management of ALF
32
33 40 and remains the only definitive treatment for patients who fail to demonstrate spontaneous recovery
34
35 41 (7). A large proportion of patients with ALF in both high and low resource settings, however, are deemed
36
37 42 to have contraindications to transplantation or deteriorate beyond transplantation before a liver donor
38
39 43 is found (8-10).

40
41 44 The burden of viral-induced ALF around the world still remains unclear, with little to no data collected
42
43 45 regarding the disease incidence (3). Establishing the etiology of viral-induced ALF is important for early
44
45 46 initiation of treatment, determining the prognosis of the liver failure and identifying potential
46
47 47 contraindications to liver transplantation. Most importantly, understanding the epidemiology of vaccine-
48
49 48 preventable etiologies of ALF should be prioritised in under-resourced regions with limited access to
50
51 49 facilities for transplantation. This review aims to synthesize data on the relative contribution of different
52
53 50 viruses to the etiology of viral-induced ALF in attempt to compile evidence that is currently missing in
54
55 51 the field.

56
57 52 *Bernal et al. 2010* completed a review of the burden of acute and fulminant liver failure based on
58
59 53 literature published between 1997 and 2009. The review became the bases for guidelines for clinical

1
2
3 54 practice (5). In this systematic review, we assess whether data have changed following the Bernal
4
5 55 publication, and whether there is evidence to warrant a review of clinical practice.
6
7

8 56 **Objectives**

- 9 57 • To estimate the prevalence of hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus
10 58 (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex
11 59 virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19,
12 60 human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6),
13 61 cytomegalovirus (CMV), coxsackievirus (CA16) and/or adenovirus (HAdVs) among patients with
14 62 ALF.
- 15 63 • To estimate the mortality rate for cases of ALF following infection with HAV, HBV, HCV, HDV,
16 64 HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs
- 17 65 • To estimate the prevalence and incidence of liver transplantation for cases of ALF following
18 66 infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV,
19 67 HHV-6, CMV, CA16 and/or HAdVs
20 68

21 69 **Methods**

22 70 This systematic review was registered with PROSPERO (registration number CRD42017079730) and the
23 71 methods for its conduction have been published (11). The results of the review are reported using the
24 72 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines checklist.
25 73

26 74 **Study eligibility criteria**

27 75 Published cross-sectional, surveillance and cohort studies reporting the outcomes of interest in patients
28 76 with ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvo-virus B19,
29 77 HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs were eligible for inclusion in this study. Studies were
30 78 eligible for inclusion if they had clearly stated case definitions of viral-induced ALF and confirmed ALF
31 79 cases using both clinical and serological, molecular or culture diagnostic methods.
32 80

33 81 **Search strategy**

34 82 A combination of the following search terms (including the use of Medical Subject Headings (MESH))
35 83 was used and adapted for each of the relevant electronic databases: epidemiology, prevalence,
36 84 incidence, burden, mortality, morbidity, fulminant hepatic failure, fulminant liver failure, acute hepatic
37

1
2
3 85 failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV),
4
5 86 hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex virus-1 (HSV1),
6
7 87 herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses
8
9 88 (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), coxsackie virus
10
11 89 and adenovirus.
12

13 90
14 91 The following electronic databases were searched for relevant literature published from 2009 to 2019:
15 92 EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The search was run on 9 April 2019 and
16 93 updated via PubMed on 30 September 2019 with no new eligible studies to include.
17
18 94

19 95 **Data extraction**

21 96 Study characteristics and outcomes of interests were extracted from the included studies on a pre-
22 97 designed data extraction form by two independent reviewers (JP and HH). Prior to use by the two
23 98 reviewers, the reliability of the extraction form was assessed by piloting 10 randomly selected articles
24 99 that met the inclusion criteria. The study team resolved any disagreements in data extraction through
25 100 consensus in consultation with RM. In cases where studies were in German, HH provided translation. In
26 101 cases where studies were not available in English or German, google translate was used to translate the
27 102 article to English (12).
28
29

30 103 31 104 **Data synthesis and analysis**

32 105 A random-effects model was fitted to the study data as it included data taken from a series of
33 106 independently performed studies in different populations. We assessed heterogeneity by calculating I^2
34 107 statistics (threshold $I^2 > 40\%$). The values of I^2 were categorized for heterogeneity as follows: “not
35 108 important” ($\leq 40\%$), “moderate” ($> 40\%$ to $\leq 60\%$) and “considerable” ($> 60\%$ to $\leq 80\%$) and
36 109 “substantial” ($> 80\%$ to $\leq 100\%$). Where “not important” or “moderate” heterogeneity existed
37 110 between studies ($I^2 \leq 60\%$), pooled outcome measures were reported with 95% confidence intervals for
38 111 each respective outcome. Where “considerable” or “substantial” heterogeneity exists between studies
39 112 ($I^2 > 60\%$), forest plots and prevalence ranges calculated using the random-effects model were used to
40 113 narratively describe each outcome.
41
42
43
44
45
46
47
48
49
50
51
52

53 114 54 115 **Risk of bias assessment**

1
2
3 116 Each included study was assessed for risk of bias and quality using the Hoy *et al.*, 2012 tool for
4
5 117 observational studies (13, 14). Studies were judged as having 'low risk' if scored 8-10, 'moderate risk' if
6
7 118 scored 5-7 and 'high risk' if scored 0-5. All risk of bias judgements were made by both JP and HH. In case
8
9 119 of disagreement in risk of bias and quality assessment, a final decision was made through consensus in
10
11 120 consultation with RM.
12

11
12

13 122 **Patient and public involvement**

14
15 123 This review was developed as part of an ongoing project by the research team that aims to generate
16
17 124 evidence to facilitate evidence-based decision-making of introducing routine hepatitis A vaccination in
18
19 125 South Africa. The findings of this review contribute to the knowledge base that aims to enhance global
20
21 126 vaccination strategies against viral-associated ALF. As this is a systematic review, no patient involvement
22
23 127 was required; however, it is hoped that the findings of this review will help to highlight the burden that
24
25 128 ALF places on populations without routine vaccination.

25
26

27 130 **Results**

28
29 131 The initial database searches yielded 6,952 records, from which 3,545 duplicates were removed. A
30
31 132 further 3,263 were excluded following the screening of titles and abstracts (**Figure 1**). The full text of the
32
33 133 remaining 144 records were screened by JP and HH, from which 25 studies were deemed to meet the
34
35 134 final inclusion criteria. Twenty-four (96%) of the included studies were cohort studies. As detailed in
36
37 135 **Table 1**, the included studies were published between 2009 and 2017. Included studies were conducted
38
39 136 globally, with 7 studies and 3 studies conducted in India and Pakistan, respectively. The populations
40
41 137 represented by the included studies spanned all age groups and included participants primarily from
42
43 138 hospital settings. As the data in this review was sourced from a variety of countries, age groups and
44
45 139 settings, the heterogeneity was considerable and/or substantial for all results. Thus, we narratively and
46
47 140 graphically reported estimates of combined prevalence rates and the spreads of prevalence.

45
46

47 142 **Vaccine-preventable viral-induced ALF**

48
49 143 We narratively report the prevalence of HAV- and HBV-induced ALF by country immunization status. The
50
51 144 point prevalence of HAV-induced ALF in countries with no routine HAV immunization at the time of data
52
53 145 collection ranged from 2% to 81% with a combined of 27% (95% CI 13, 43), while the prevalence in
54
55 146 countries with routine HAV immunization at the time of data collection ranged from 1% to 2% with a
56
57 147 combined of 2% (95% CI 1, 3) (**Figure 2**). In Argentina, the prevalence of HAV-induced ALF prior to

5
58

1
2
3 148 routine immunization was approximately 50% (95% CI 45, 55), compared to approximately 1% (95% CI 0,
4 149 5) after immunization was introduced. The point prevalence of HBV-induced ALF in countries without
5 150 universal HBV immunization at the time of data collection ranged from 16% to 27% with a combined of
6 151 22% (95% CI 16, 30) (**Figure 3**). The point prevalence of HBV-induced ALF in countries with universal HBV
7 152 immunization at the time of data collection ranged from 0% to 83% with a combined of 20% (95% CI = 8,
8 153 35).

13 154

15 155 **ALF attributable to non-vaccine-preventable viral infections**

16 156 The point prevalence of HCV-induced ALF ranged from 2% to 25% with a combined of 9% (95% CI = 1,
17 157 21) (**Supplementary Figure 1**). The point prevalence of HEV-induced ALF ranged from 3% to 70% with a
18 158 combined of 32% (95% CI 24, 41) (**Supplementary Figure 2**). The point prevalence of HDV-, HHV/HSV-,
19 159 CMV-, and EBV-induced ALF were estimated to have combined prevalences of 4% (95% CI 0, 13), 6%
20 160 (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%
21 161 (95% CI 0, 5), respectively (**Supplementary Figure 3**). Data was not available to estimate the burden of
22 162 ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and/or HAdVs as outlined per the published
23 163 protocol (11).

29 164

31 165 **Outcomes of viral-induced ALF**

32 166 The narratively reported outcomes of viral-induced ALF were found to be severe. The mortality rates
33 167 associated with viral-induced ALF in lower-middle income countries ranged from 18% to 91% with a
34 168 combined mortality rate of 50% (95% CI 36, 64) (**Figure 4A**). The mortality rates associated with viral-
35 169 induced ALF in upper-middle income countries ranged 3% to 45% with a combined mortality rate of 26%
36 170 (95% CI 1, 63) (**Figure 4A**). The mortality rates associated with viral-induced ALF in high income countries
37 171 ranged from 12% to 40% with a combined mortality rate of 29% (95% CI 17, 43) (**Figure 4A**). The rate of
38 172 encephalopathy associated with viral-induced ALF cases in children ranged from 69% to 100% with a
39 173 combined rate of 89% (95% CI 79, 97) (**Figure 4B**). The need for liver transplantation with viral-
40 174 associated ALF ranged from 4% to 62% with a combined rate of 25% (95% CI 6, 53) (**Figure 4B**). The need
41 175 for renal transplant in viral-associated ALF cases ranged from 4% to 34% with a combined rate of 18%
42 176 (95% CI 2, 43) (**Figure 4B**).

51 177

53 178 **Methodological quality**

54

55

56

57

58

59

1
2
3 179 Risk of bias scores were assigned by two reviewers (JP and HH) and are described in **Supplementary**
4
5 180 **Table 1**. Overall, a majority of the included studies were judged as having ‘low risk’ of bias. Only one
6
7 181 included study was judged as having ‘moderate risk’ of bias due to lack of clarity around the
8
9 182 representativeness of the study population to the national population, methods of participant selection
10
11 183 and methods employed to reduce the likelihood of non-response.
12

184

13 185 **Discussion**

14
15 186 This systematic review estimated the burden of ALF following infection with HAV, HBV, HCV, HEV,
16
17 187 HSV/HHV, CMV, EBV, and parvo-virus B19. The prevalence of HAV-induced ALF is markedly lower in
18
19 188 countries with routine HAV immunization while HEV was the most common etiological cause of viral-
20
21 189 induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by
22
23 190 high fatality rates, which seem to increase with poor economic status of the studied countries.
24

191

25 192 The estimated prevalence of HAV-induced ALF in countries with routine HAV immunization was
26
27 193 markedly lower than the estimated prevalence in countries without routine HAV immunization. When
28
29 194 looking at countries with data before and after the introduction of routine HAV immunization, the
30
31 195 reduction of HAV-induced ALF due to vaccination is further highlighted. The combined prevalence of
32
33 196 HBV-induced ALF was the same in settings with or without universal HBV immunization. Countries
34
35 197 without universal HBV immunization programs are likely to have weak healthcare systems; thus, the
36
37 198 reported prevalence of HBV-induced ALF is assumed to be an underestimate of the true burden in these
38
39 199 populations due to weak routine testing and reporting systems. Currently, there is one HEV vaccine
40
41 200 (Hecolin) licensed in China that has shown promise with a high degree of efficacy in preventing HEV
42
43 201 genotype IV infection in healthy individuals 16 to 65 years (15). Further exploration of the efficacy of this
44
45 202 vaccine for prevention of infection with genotypes I and II in different populations should to explore it’s
46
47 203 application in different countries and HEV endemicity settings (16).
48

204

49 205 This review estimated the mortality rate for viral-induced ALF to be approximately 50% in low- and
50
51 206 middle- income countries (LMICs) and less than 30% in upper-middle- and high-income countries.
52
53 207 Previous studies have estimated that mortality rates associated with ALF vary between 60% and 80%,
54
55 208 depending on the disease etiology as well as a patient’s access to care. Our review shows that although
56
57 209 viral-induced ALF still carries a significant mortality, though possibly lower than that reported for other
58
59 210 ALF etiologies (5, 6). Mortality data largely comes from hospitals with the capacity to diagnose viral-

7

1
2
3 211 induced ALF, thus deaths outside of the hospital system or ALF deaths without virological testing may
4
5 212 not be captured in these mortality estimates. Liver transplantation is required by approximately 25% of
6
7 213 viral-induced ALF cases and approximately 18% of viral-induced ALF cases required renal
8
9 214 transplantation, globally. In addition to general lack of resources for transplantation, a significant
10
11 215 proportion of potential candidates have contraindications to transplant related to poor socioeconomic
12
13 216 status in LMICs. The transplant data included in this review may only reflect successful and unsuccessful
14
15 217 transplants, not those that were needed but not carried out due to resource constraints or
16
17 218 contraindications.

18
19 219
20 220 This review is limited by lack of data for some of the viral etiologies of ALF including for VZV, HPIVs, YFV,
21
22 221 CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced
23
24 222 ALF. Additionally, we believe that our findings underestimate the global burden of viral-induced ALF as
25
26 223 some important causes of ALF (e.g. HSV/HHV) are believed to be underrecognized as they require PCR
27
28 224 testing for diagnosis. The included studies also used varying methods of virus detection including
29
30 225 serology and molecular tests which further added to the heterogeneity in the results of our review. This
31
32 226 is a well-recognized limitation in studies of ALF where diagnostics are often limited by cost in under-
33
34 227 resourced regions where viral causes of ALF are more prevalent. The limited availability of data,
35
36 228 including lack of same country data on burden of disease before and after introduction of immunization,
37
38 229 hindered most of the planned sub-group analyses outlined in the study protocol. Where data were
39
40 230 available, high heterogeneity of the data led to planned meta-analyses and meta-regression analyses
41
42 231 not being possible. Lastly, the diversity of viruses attributable to ALF cases led to low statistical power in
43
44 232 meta-analyses conducted.

45
46 233
47 234 Future research should assess the burden of viral-induced ALF following infection with HDV, VZV, HPIVS,
48
49 235 YFV, CA16 and HAdVs. Collectively, high-quality data on all viral etiologies of ALF would allow for better
50
51 236 pooling of results. The review team encourages future studies to incorporate health economic estimates
52
53 237 and mathematical modelling where data permits to assist health policy decision-makers to better design
54
55 238 strategies for the prevention and management of viral-induced ALF. Epidemiological-economic
56
57 239 modelling of immunization against HAV, HBV and HEV may well show that introduction of vaccination
58
59 240 could lead to future cost savings in the long run due to prevented medical care and liver failure.

60 241

242 **Conclusions**

1
2
3 243 We successfully addressed the aim of the study although data on VZV, HPIVs, YFV, CA16 and/or HAdVs
4
5 244 were missing. Notwithstanding the noted limitations, it is clear that HAV, HBV and HEV – vaccine-
6
7 245 preventable ALF etiologies – account for a large proportion of ALF (approximately 21%, 20%, 32% of
8
9 246 viral-induced ALF cases, respectively). The burden of ALF that is associated with vaccine-preventable ALF
10
11 247 etiologies should be used in conjunction with other available key evidence to inform practice and
12
13 248 policies on immunization, particularly in LMICs. A majority of LMICs have established universal
14
15 249 vaccination against HBV. The World Health Organization has recently recommended the introduction of
16
17 250 an HBV birth dose which is aimed at elimination of the virus and, if successful, will subsequently reduce
18
19 251 the burden of HBV-induced ALF. Routine HAV immunization in LMICs, however, are lacking. More data is
20
21 252 urgently needed to guide routine use of the vaccine in prevention of morbidity and mortality caused by
22
23 253 the virus. Lastly, further applicability of HEV vaccines should be explored, especially in LMICs where
24
25 254 resources for managing viral-induced ALF are glaringly lacking.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

256 Contributors

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

262 Funding

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

266 Competing interests

267 None declared.

268 Data availability

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

270 Patient consent for publication

271 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 agreement. *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 AI 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.

- 1
2
3 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.
- 4 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.
- 5 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.
- 6 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.
- 7 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.
- 8 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.
- 9 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.
- 10 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.
- 11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

FIGURE LEGENDS

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	<i>Acute Liver Failure Study Group Germany</i> 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

1								
2								
3								
4								Onset of coagulopathy and/or
5								encephalopathy ≤ 4 weeks
6								after the onset of symptoms,
7	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	a prothrombin time > 2, an increased bilirubin and evidence for liver failure complicated by encephalopathy
11								
12								
13								<i>Mieli-Vergani</i> case definition:
14								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)
15								
16								
17								
18	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	
19								
20								
21								
22								
23								
24								
25								
26	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
27								
28								
29								
30								Elevated ALT levels or AST of at least five-fold with clinical jaundice and without evidence of chronic liver disease.
31								Patients who had INR > 1.5 with encephalopathy or INR > 2 without encephalopathy
32	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	
33								
34								
35								
36								
37								
38								
39								International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 570.0
40	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	
41								
42								
43								
44								
45								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
46								
47								
48	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	
49								
50								
51								
52								
53								
54								
55								
56								
57								
58								
59								
60								

1								
2								
3								
4								Previously healthy patients
5								who presented with severe
6								impairment of hepato-cellular
7	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	function, i.e. encephalopathy, coagulopathy, and jaundice, within six months of onset of symptoms
8								
9								
10								
11								
12								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
13								
14								
15	Manka et al., 2015 (28)	Retrospective cohort	To investigate the causes of previously diagnosed indeterminate cases ALF	Germany	High	6-Nov	13-Dec	
16								
17								
18								
19								
20								
21								
22								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
23								
24	Mendizabal et al., 2014 (29)	Retrospective cohort	To determine the causes and short-term outcomes of ALF	Argentina	High	5-Jun	11-Dec	
25								
26								
27								
28								
29								
30								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
31								
32	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	
33								
34								
35								
36								
37								
38								
39								
40	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
41								
42								
43								
44								
45								
46								
47								
48								
49								Onset of encephalopathy \leq 28 days after the onset of symptoms with INR > 2 and increased bilirubin complicated by encephalopathy in patients
50	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	
51								
52								
53								
54								
55								
56								
57								
58								
59								
60								

							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	<i>International Association for the Study of the Liver</i> 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 \geq 15 s or INR \geq 1.5 in the presence of clinical HE or a PT \geq 20 s or INR \geq 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	<i>International Association for the Study of Liver</i> (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	<i>United States Acute Liver Failure Study Group</i> 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 \leq 40% or INR \geq 1.5 excluding hematologic diseases] and jaundice [Tbil \geq 171 μ mol/L] within 4 weeks in a child without pre-existing liver diseases
<p>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</p>								

Figure 1: Flow diagram for selection of studies

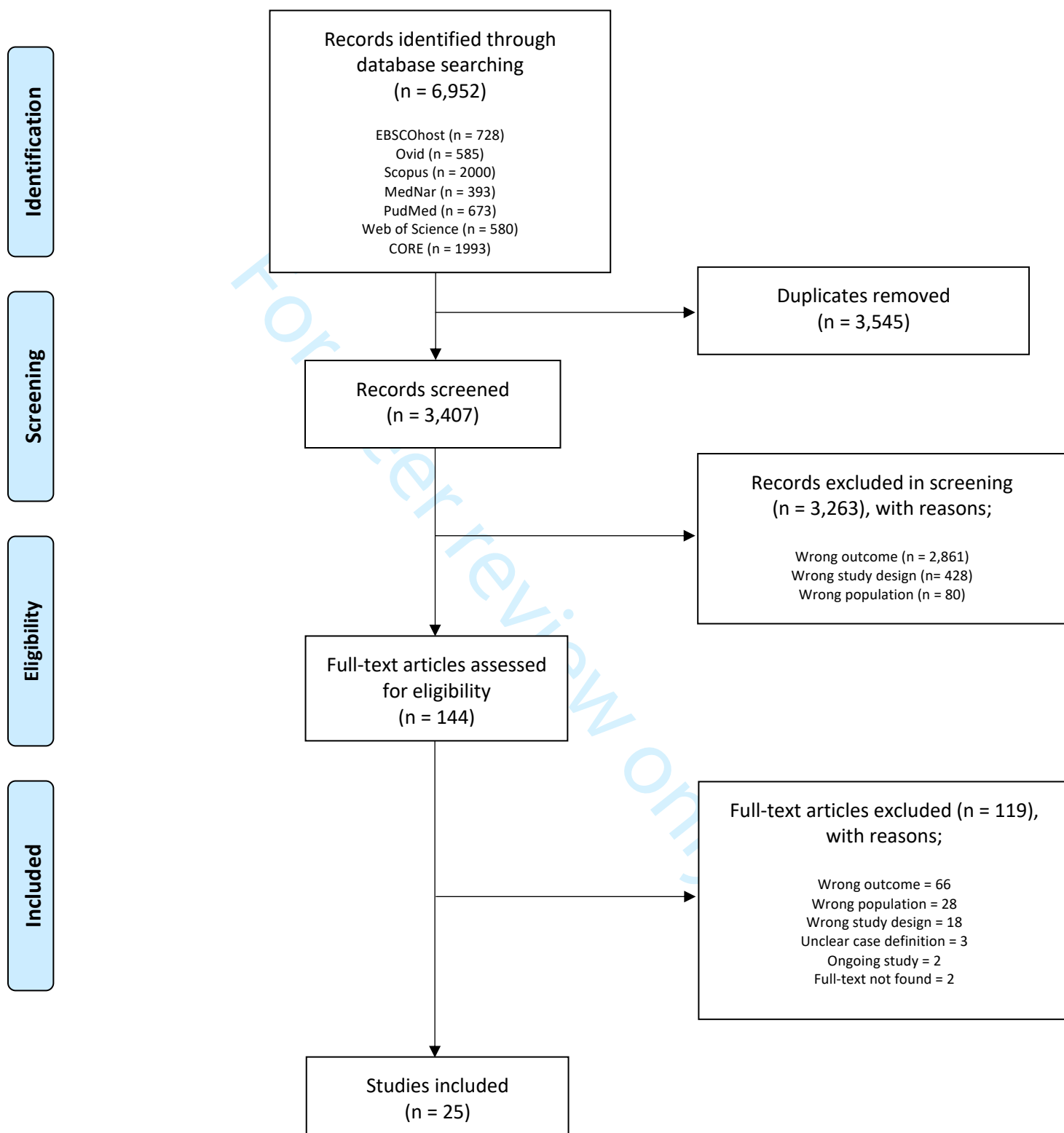


Figure 2: Prevalence of HAV-induced ALF by country HAV immunization status

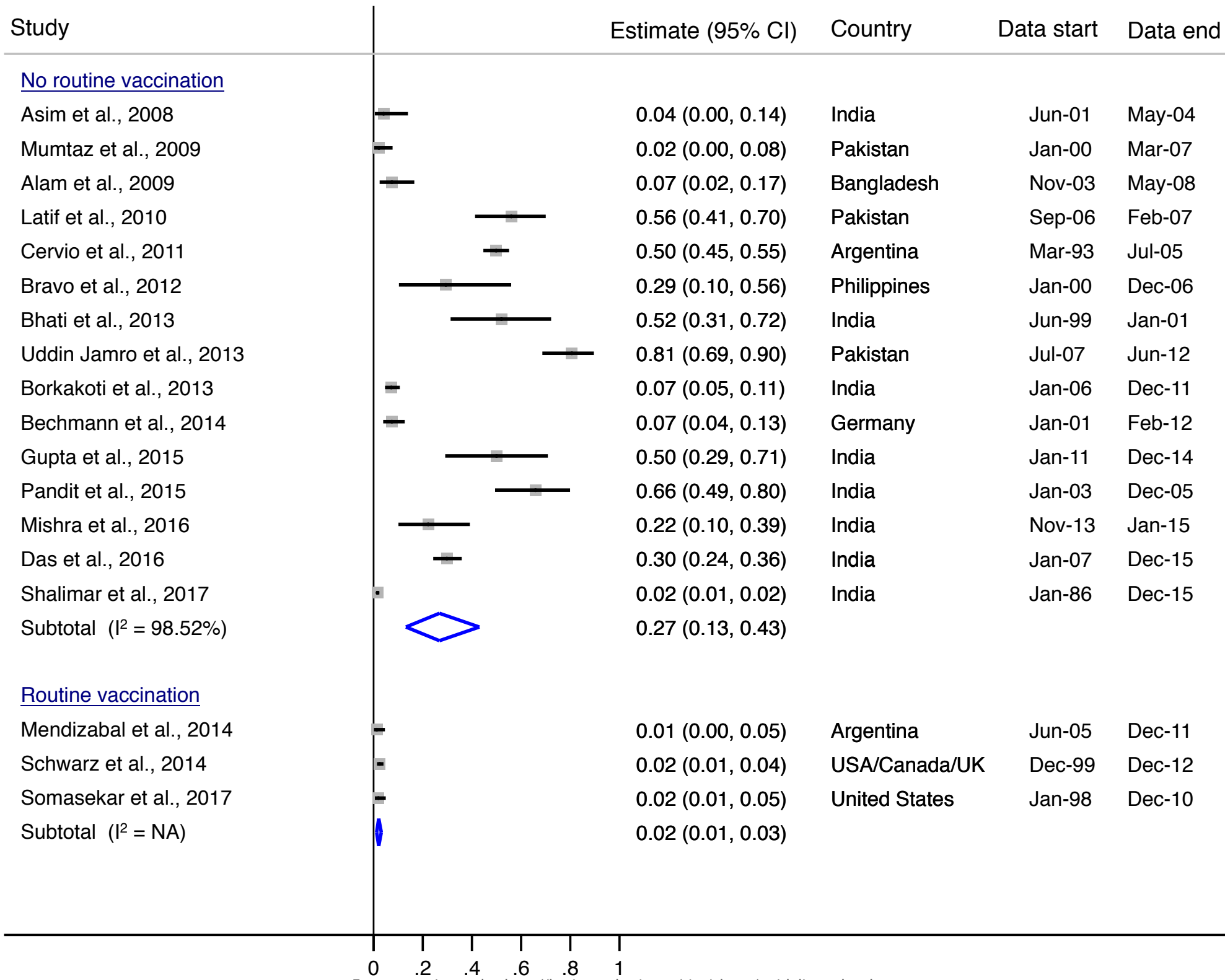


Figure 3: Prevalence of HBV-induced ALF by country HBV immunization status

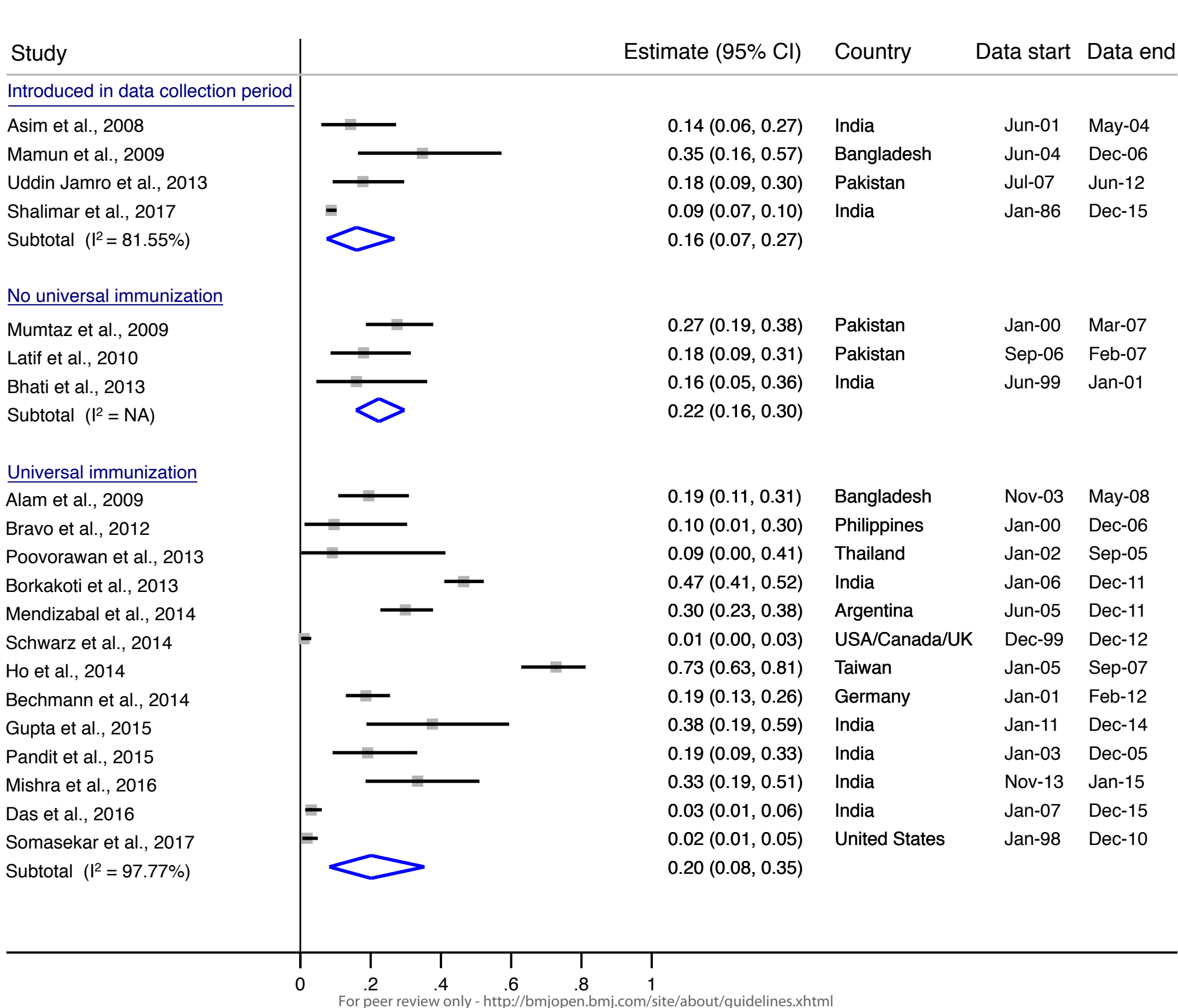
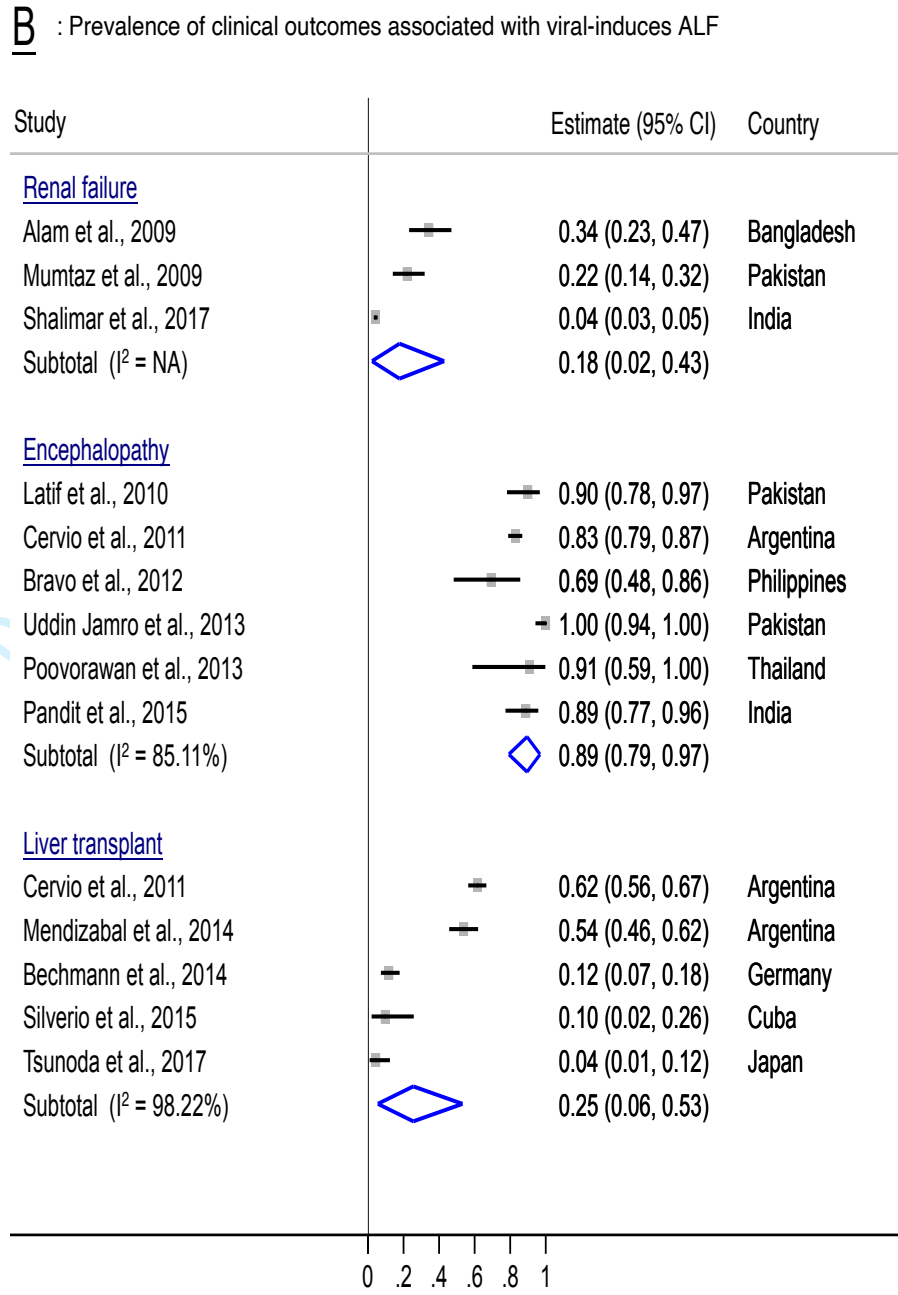
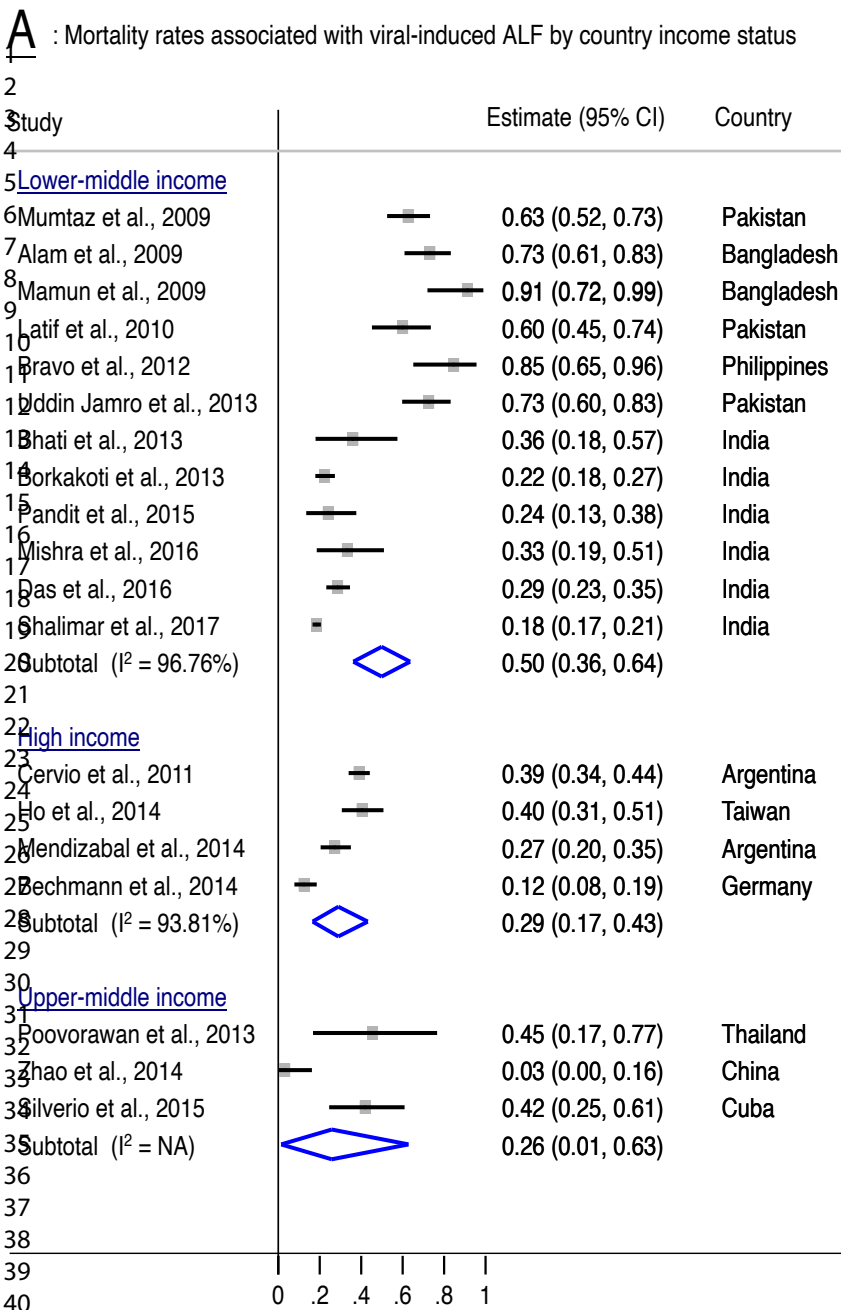
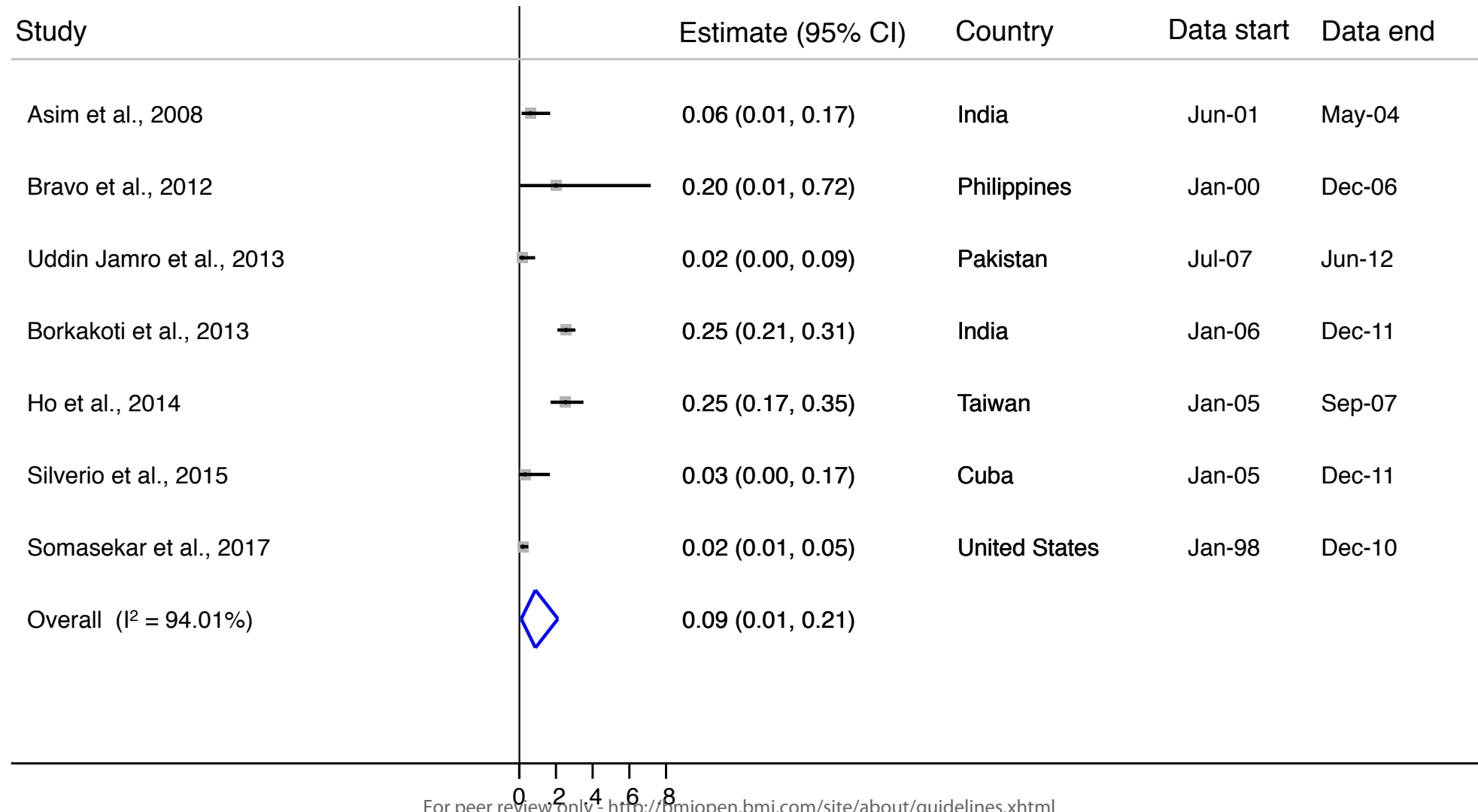


Figure 4: Prevalence of outcomes associated with viral-induced ALF



Supplementary Figure 1: Prevalence of HCV-induced ALF

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

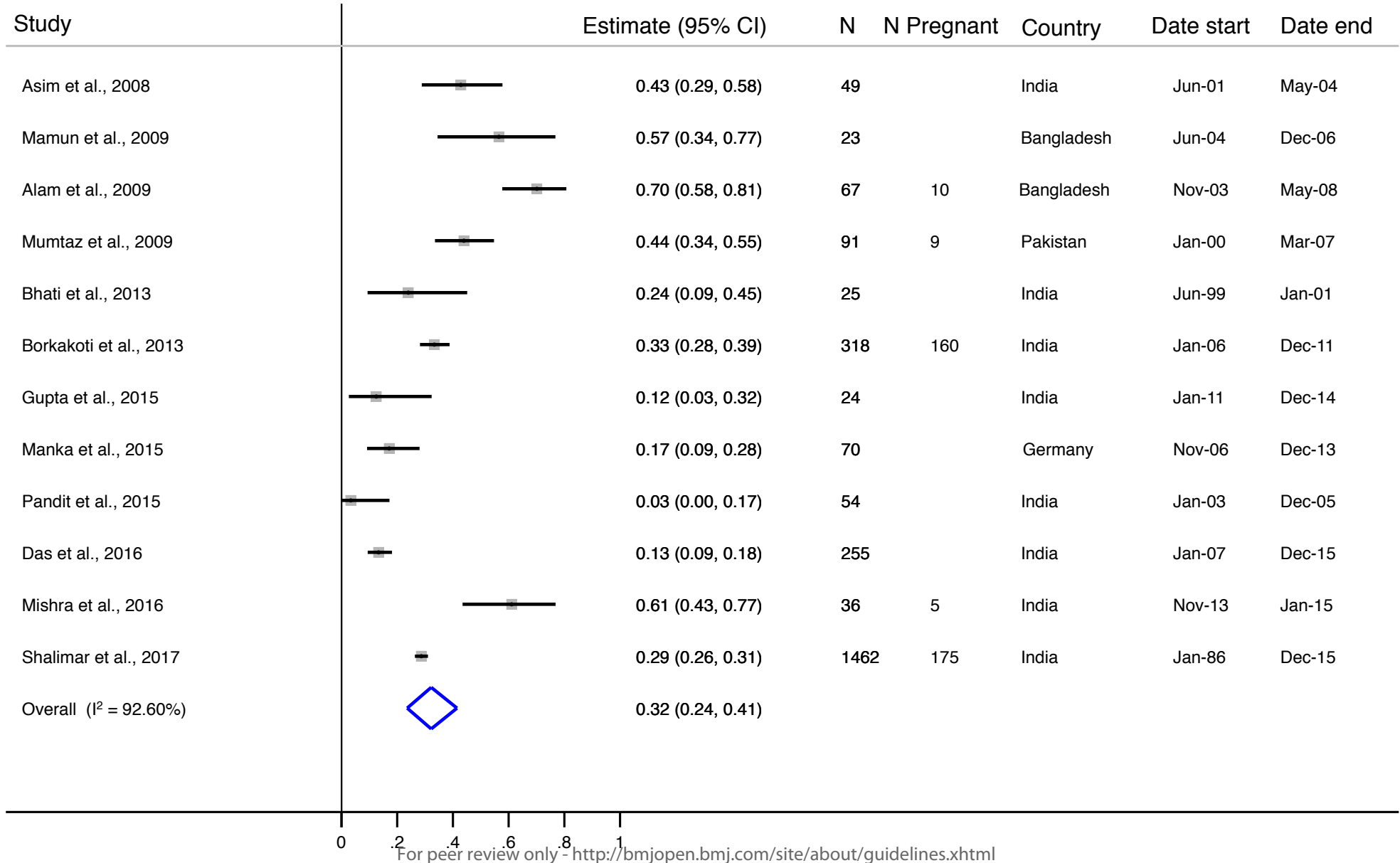


For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Abbreviations: HCV = hepatitis C virus, ALF = acute liver failure, CI = confidence interval, I² = heterogeneity statistic

Supplementary Figure 2: Prevalence of HEV-induced ALF

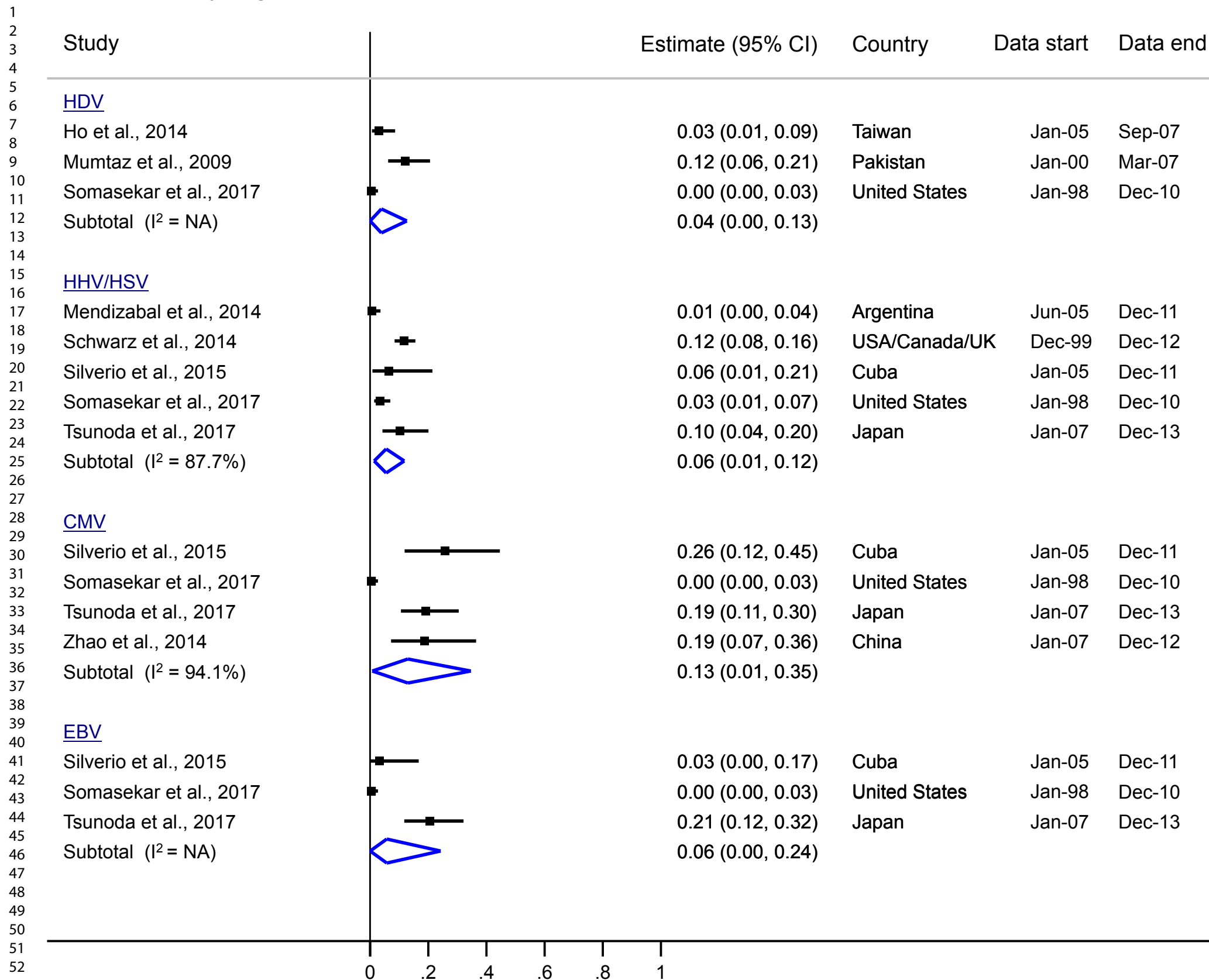
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Abbreviations: HEV = hepatitis E virus, ALF = acute liver failure, CI = confidence interval, I² = heterogeneity statistic

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



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

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	Represent ation of the national populatio n	Represent ation of target populatio n	Rand om select ion or censu s	Minim al likelih ood of non- respon se bias	Data collecte d directly from particip ants	Accept able case definiti on	Valid measure ment	Same mode of data collect ion	Appropri ate length	Appropri ate numerator (s) and denomina tor(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	Yes	10
Tsunoda et al., 2017	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Zhao et al., 2014	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8

For peer review only

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

Page 1 of 2

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
Page 1 of 2			
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



PRISMA 2009 Checklist

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

Page 2 of 2

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47